DIAZO PHOSPHONATES AS USEFUL SYNTHETIC INTERMEDIATES FOR TOTAL SYNTHESIS

by

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STATEMENT OF DISSERTATION APPROVAL

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, and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

A series of acceptor-acceptor type diazo phosphonates were successfully synthesized. When exposed to $Rh_2(OAc)_4$, depending on their substitution patterns, vinyl diazo phosphonates underwent either sulfonium ylide rearrangements or C-H insertion reactions to provide C-3 quaternary indolines or cyclopentenes, respectively. Diazo vinyl phosphonates, on the other hand, reacted with alcohols, amines and thiols in the presence of a Rh catalyst to generate vinyl ethers, enamines and vinyl sulfides. Intramolecular cyclization of the resulting vinyl ethers led to the formation of oxetanes and furans. This O-H insertion/ intramolecular cyclization strategy was utilized in the synthesis of the phosphonate analog of dysiherbaine.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ABSA	4-acetamidobenzenesulfonyl azide
Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
Et	ethyl
HMPA	hexamethylphosphoric acid triamide
HOBt	1-hydroxybenzotriazole
IR	infrared spectroscopy

LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
m-CPBA	*meta* chloroperbenzoic acid
Me	methyl
Ms	methanesulfonyl
MS	mass spectrometry
NaHMDS	sodium hexamethyldisilazane
NMO	*N*-methylmorpholine
NMPA	*N*-(3-methoxypropyl)acrylamide
NMR	nuclear magnetic resonance
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
rt	room temperature
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl

ACKNOWLEDGEMENTS

The last six years have been such an amazing journey. Now when I look back, I first want to thank my advisor Jon Rainier. I learned so much from him, not only the knowledge of organic synthesis but also the capability to conduct scientific research. I am so glad that together we accomplished some really interesting chemistry. My committee members Dr. Sigman, Dr. Ji, Dr. Keck, Dr. Davis and Dr. Woycechowsky gave me a lot of valuable advice and I appreciate it very much. I am very thankful that Dr. Boyarskikh introduced me to the diazo phosphonate project.

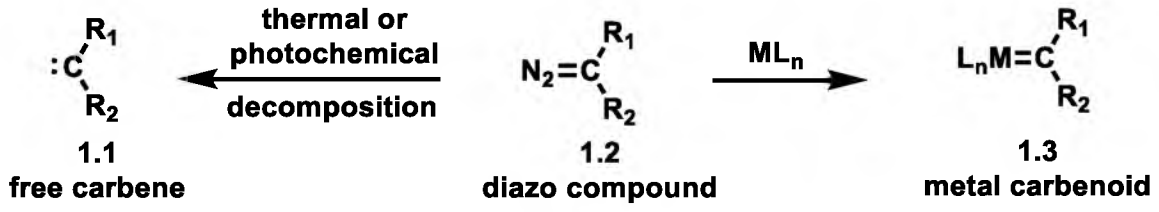
I am fortunate to have a wonderful family. My parents always supported me and encouraged me to pursue my dreams. I met my perfect wife four years ago and we had our little girl last year, which is the most amazing thing that has happened in my life. I feel very blessed with so much love around me and for which I will always be grateful.

CHAPTER 1

INTRODUCTION

1.1 Metal carbenoids: a general introduction

Diazo compounds are powerful and versatile intermediates in synthetic chemistry because highly reactive carbenes can be formed by the loss of dinitrogen. Compared to free carbenes **1.1** generated thermally or photochemically, metal carbenoids **1.3** generated from metal salts and diazo compounds **1.2** are generally much more selective and efficient when reacting with nucleophiles (Scheme 1.1).[1] In addition, usually only a catalytic amount of metal salt is needed. A number of synthetically unique transformations such as cyclopropanations, X-H (X = O, N, S, etc.) insertions, C-H insertions and ylide formations can be accomplished when treating the metal carbenoids with different nucleophiles.[2]

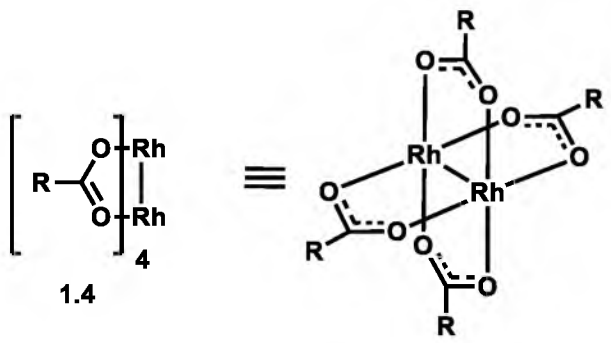


Scheme 1.1 Free carbene vs metal carbenoid

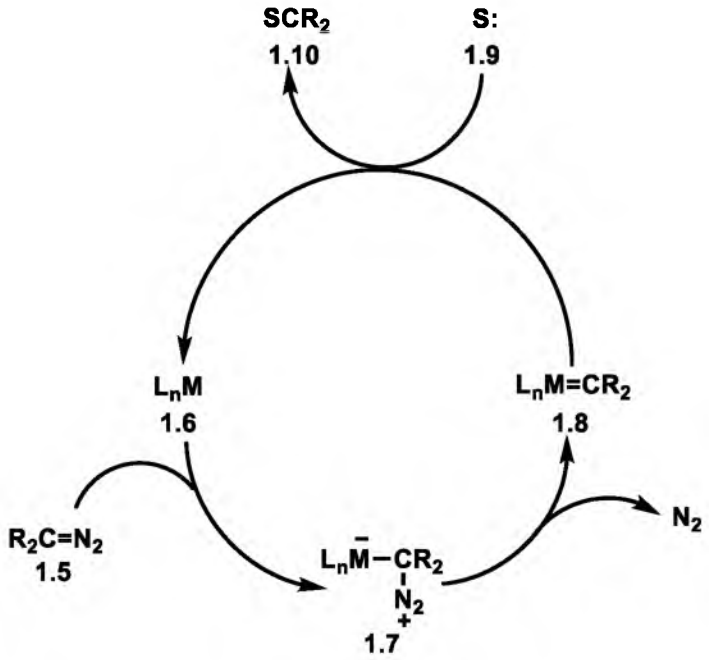
The earliest catalysts applied to diazo decomposition were copper salts.[3] Although copper bronze, copper(I) and copper(II) salts can all be used as catalysts for this reaction, it is now established that copper(I) species are the active catalysts during the reaction.[4] However, it was not until the *C4*-symmetric dirhodium tetracarboxylate catalysts **1.4** were discovered that metal carbenoid chemistry experienced exponential progress (Scheme 1.2).[5] Compared to the traditional copper catalysts, the dirhodium catalysts are usually more efficient in terms of yields. In addition, rhodium catalysts are generally more versatile because the electronic and steric properties of the tetracarboxylate ligands can be easily tuned allowing for the generation of metal carbenoids with different reactivity profiles.[6]

Numerous experiments have been carried out in order to understand the mechanism of catalytic diazo decomposition, metal carbenoid generation and subsequent reactions. It is now believed that the metal catalyst first serves as a Lewis acid to form the diazonium ion adduct **1.7**, of which the metal center donates a pair of electrons back to the adjacent carbon to form the metal carbenoid **1.8** by the loss of the dinitrogen. The reaction of the electrophilic carbene moiety with an electron-rich substrate regenerates the metal catalyst (Scheme 1.3).[7]

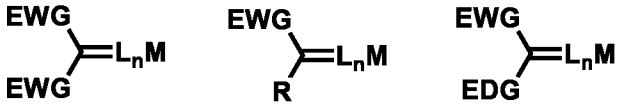
Generally, there are three types of metal carbenoids: acceptor, acceptor-acceptor and donor-acceptor type metal carbenoids (Scheme 1.4).[8] Because metal carbenoids normally display electrophilic character, acceptor and acceptor-acceptor type metal carbenoids generally are more reactive and less selective.[9]



Scheme 1.2 Dirhodium tetracarboxylate catalyst



Scheme 1.3 Mechanism of catalytic diazo decomposition



EWG = Electron Withdrawing Group,
EDG = Electron Donating Group,
R = H or alkyl

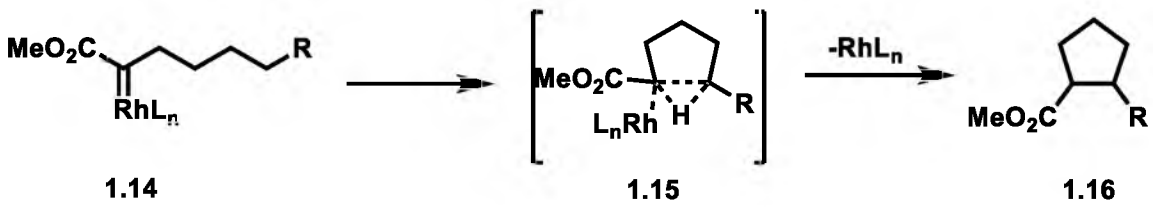
Scheme 1.4 Classification of metal carbenoids

1.2 Application of metal carbenoids in natural product synthesis

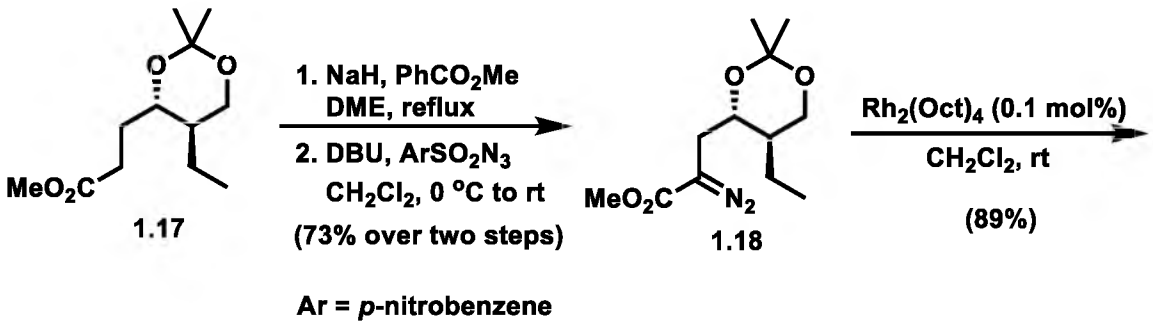
Due to their unique reactivities, metal carbenoids have been utilized in natural product synthesis since the 1980s.[10] Acceptor type metal carbenoids and acceptor-acceptor type metal carbenoids were first utilized in synthetic chemistry because of the availability and stability of their parent diazo compounds. Due to their highly electrophilic nature, these two types of metal carbenoids were mostly involved in intramolecular reactions.

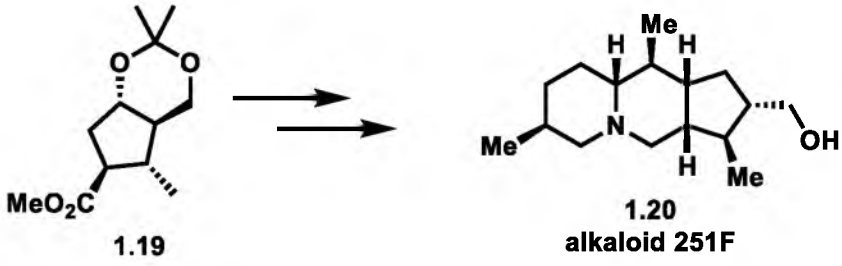
A unique reaction for metal carbenoid is the intramolecular C-H insertion, which provides a five membered ring in most cases. Mechanistically, the C-H insertion is believed to occur through a concerted mechanism when the C-C bond and C-H bond form as the metal catalyst dissociates (Scheme 1.5).[11]

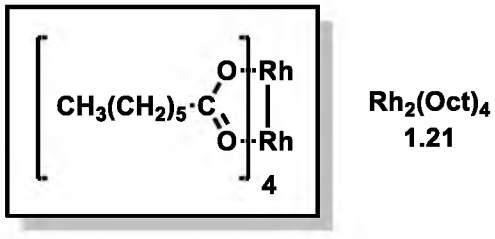
The Taber group was among the first to recognize the synthetic utility of the intramolecular C-H insertion reaction. During detailed experiments they demonstrated that high diastereoselectivity could be achieved through careful construction of the diazo substrate and elaborate selection of the metal catalyst. Their work was highlighted in the first total synthesis of alkaloid 251F (Scheme 1.6).[12] Starting from the enantiopure acetal **1.17**, β-ketoester formation facilitated the subsequent diazo transfer reaction, and diazo ester **1.18** was formed in 73% yield. The key diazo decomposition step was accomplished in the presence of $Rh_2(Oct)_4$ and provided cyclopentane **1.19** as a single diastereomer. The newly-formed stereocenters were shown to have the desired configurations of the natural product. Further functional group manipulations allowed the cyclopentane **1.19** to advance to the natural product alkaloid 251F.



Scheme 1.5 Mechanism of intramolecular C-H insertion of metal carbenoid





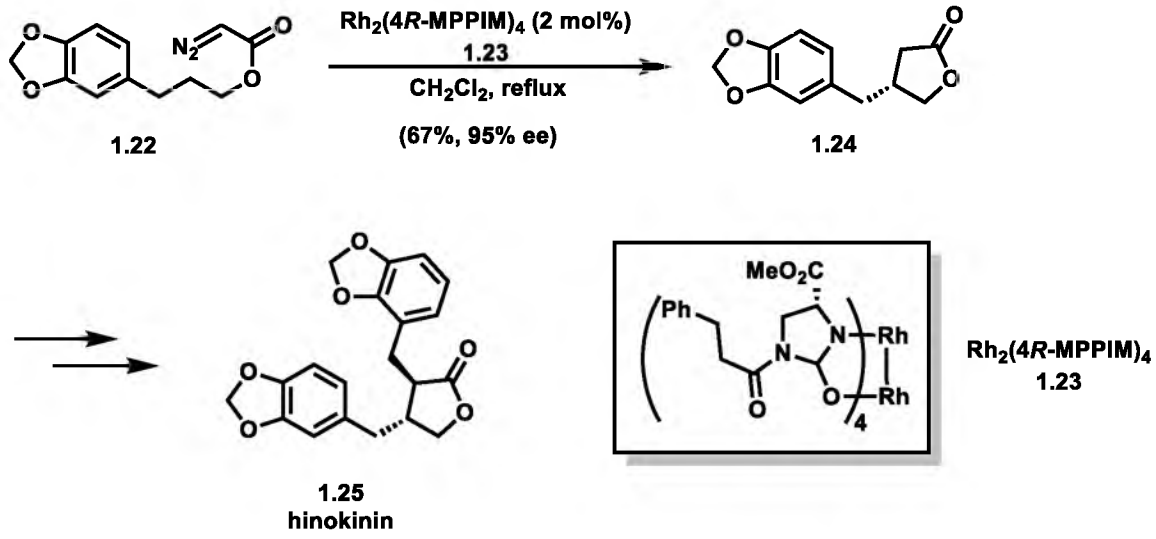


Scheme 1.6 Taber's total synthesis of alkaloid 251F

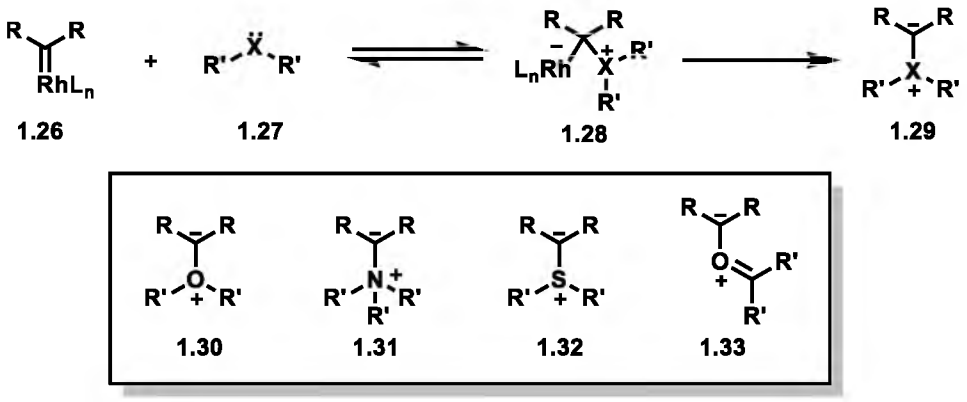
Enantioselective intramolecular C-H insertion of metal carbenoids experienced rapid growth in the 1990s, thanks to the discovery of efficient chiral rhodium catalysts including rhodium carboxylates and rhodium carboxymidates.[13] The Doyle group has developed a series of carboxymidate based dirhodium catalysts and utilized them to catalyze intramolecular C-H insertion of diazo esters. One example that illustrated the power of these transformations was the total synthesis of lignan lactones such as hinokinin (Scheme 1.7).[14] Cinnamic acid based diazo ester **1.22** was exposed to chiral rhodium catalyst **1.23** to give the desired lactone **1.24** in high yield and ee, via an intramolecular C-H insertion. Lactone **1.24** was then converted to the natural product hinokinin.

Ylide chemistry is another area where metal carbenoids show great utility.[15] Because of their highly electrophilic nature, metal carbenoids tend to react with hetero atoms to form metal associated ylides **1.28** (Scheme 1.8). The free ylides **1.29** are formed by the dissociation of the metal catalysts. Both the metal-associated ylides **1.28** and the free ylides **1.29** can serve as reactive species for subsequent reactions. Commonly used ylides include oxonium, iminium, sulfonium and carbonyl ylides **1.30** - **1.33**.

The Padwa group first demonstrated that metal carbenoids could be used to generate cyclic carbonyl ylides. They also showed that subsequent ntramolecular dipole cycloadditions would result in oxabicyclic substrates. Five and six membered cyclic carbonyl ylides were formed in most cases due to the more efficient orbital overlap between the metal carbenoid and carbonyl oxygen 5 or 6-atom away. A beautiful application of this methodology was the synthesis

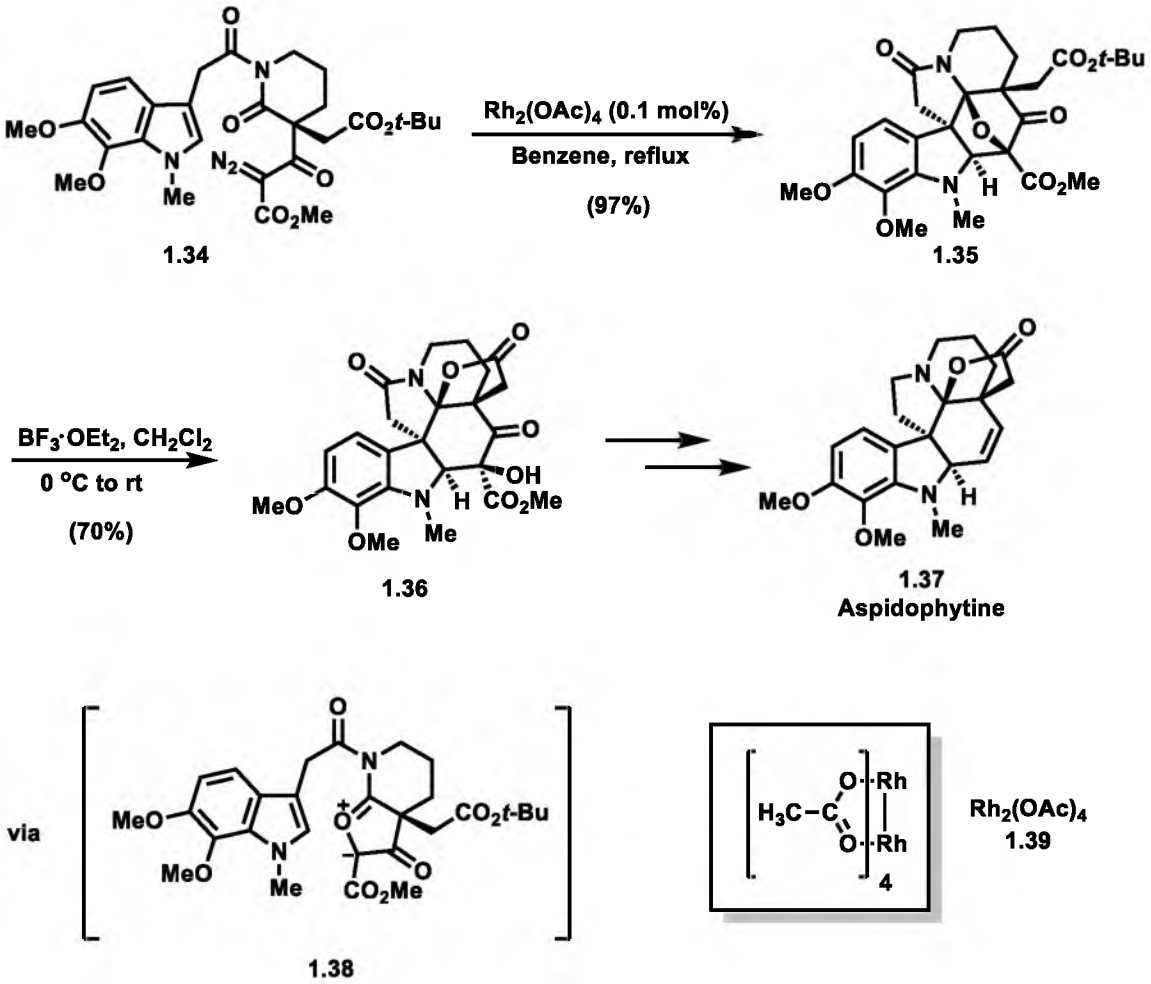


Scheme 1.7 Doyle's total synthesis of hinokinin



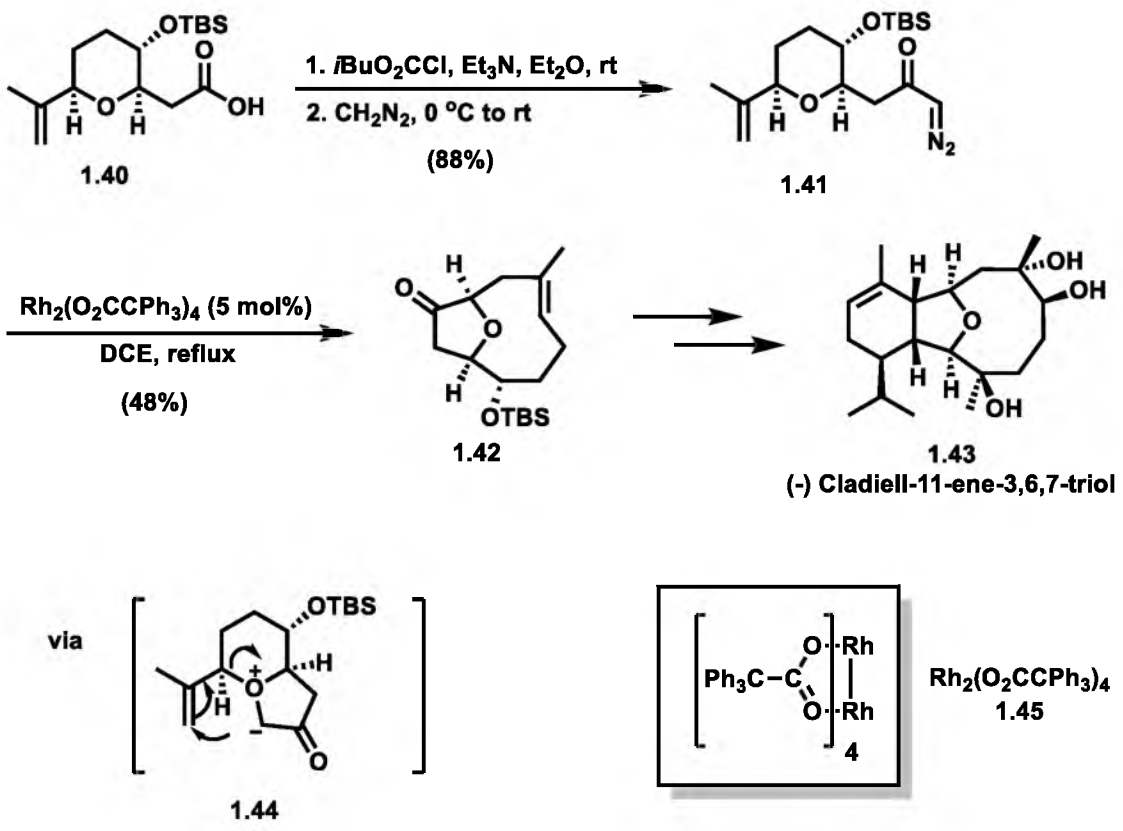
Scheme 1.8 Generation of ylide and structures of common ylides

of aspidophytine.[16] Decomposition of diazo β-ketoester **1.34** and reaction of the resulting metal carbenoid with the neighboring imido carbonyl gave the carbonyl dipole intermediate **1.38**, in situ cyclization with the tethered indolyl group provided cycloadduct **1.35** (Scheme 1.9). Treating the cycloadduct **1.35** with BF_3•Et_2O readily cleaved the oxygen bridge and gave rise to aspidophytine precursor **1.36**.



Scheme 1.9 Padwa's total synthesis of Aspidophytine

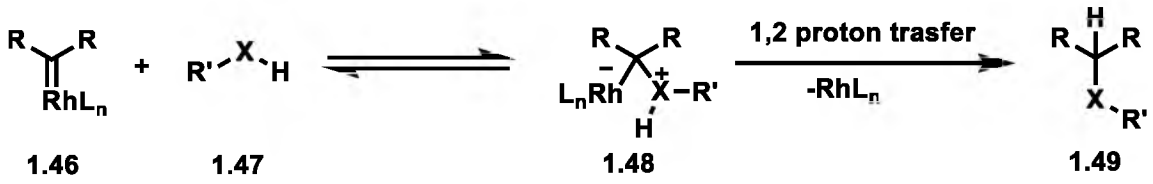
Taking advantage of a facile oxonium ylide formation between a metal carbenoid and an ether, the Clark group developed an oxonium ylide formation/ [2,3]-sigmatropic rearrangement reaction cascade to access a group of oxygen-bridged macrocycles. One excellent example is shown in Scheme 1.10.[17] Starting from acid **1.40**, diazo ketone **1.41** was obtained by first forming a mixed anhydride then reacting it with diazomethane. Diazo decomposition with $Rh_2(O_2CCPh_3)_4$ gave the alkene **1.42** via the dipolar cycloaddition of **1.44**. Furan **1.42** was advanced to the natural product (-) Cladiell-11-ene-3,6,7-triol.



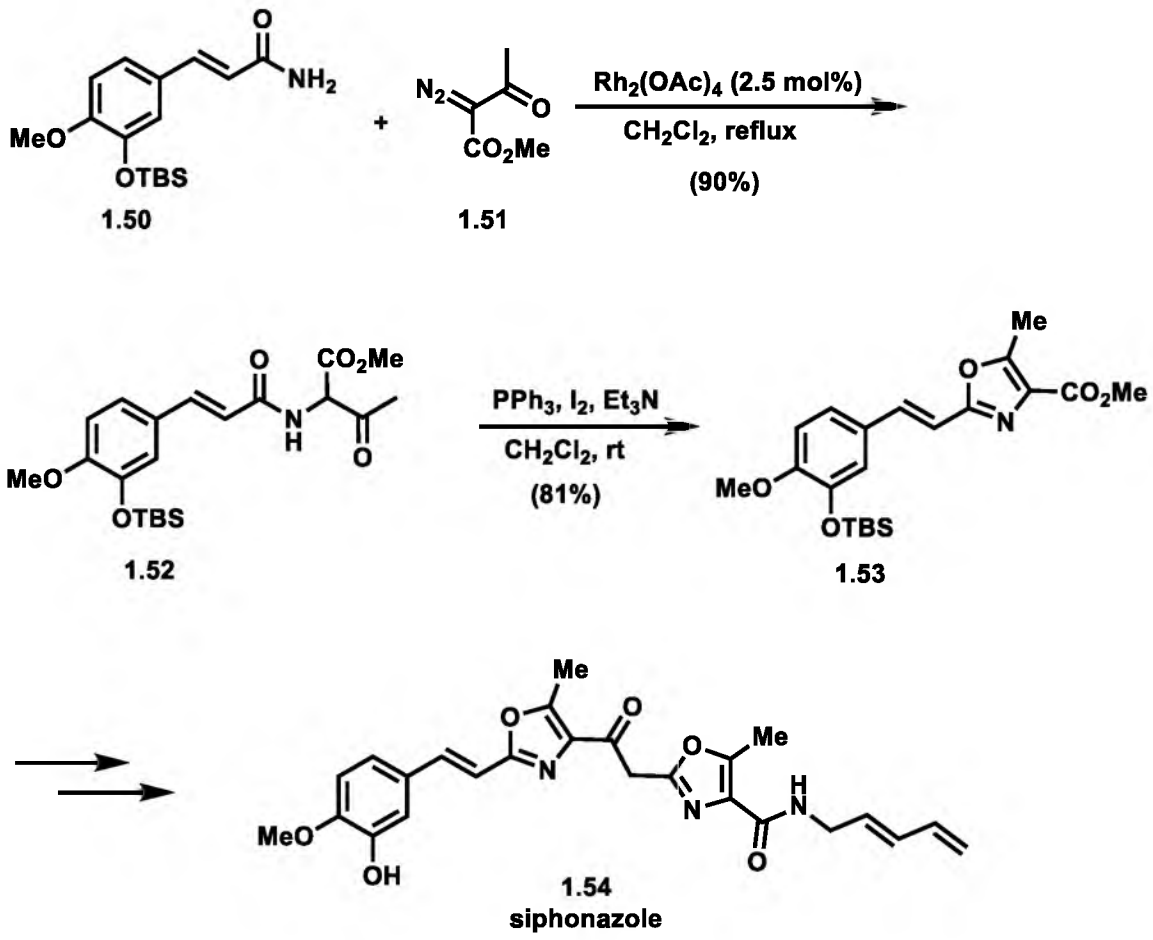
Scheme 1.10 Clark's synthesis of (-) Cladiell-11-ene-3,6,7-triol

X-H insertions occur when metal carbenoids interact with heteroatom-hydrogen bonds.[18] It has been identified to be the preferred reaction pathway of metal carbenoids. Mechanistically, X-H insertion is probably distinct from C-H insertion as an ylide **1.48** probably is formed first, and then undergoes a [1,2] proton transfer to realize the insertion product (Scheme 1.11).

Notably, the Moody group has shown that amides could readily insert into the metal carbenoid derived from diazo ketoester **1.51** to provide compound **1.52**, which then cyclized upon oxidation condition using PPh_3/I_2 to form oxazole **1.53** (Scheme 1.12).[19] This chemistry was carried out to complete the total synthesis of siphonazole.



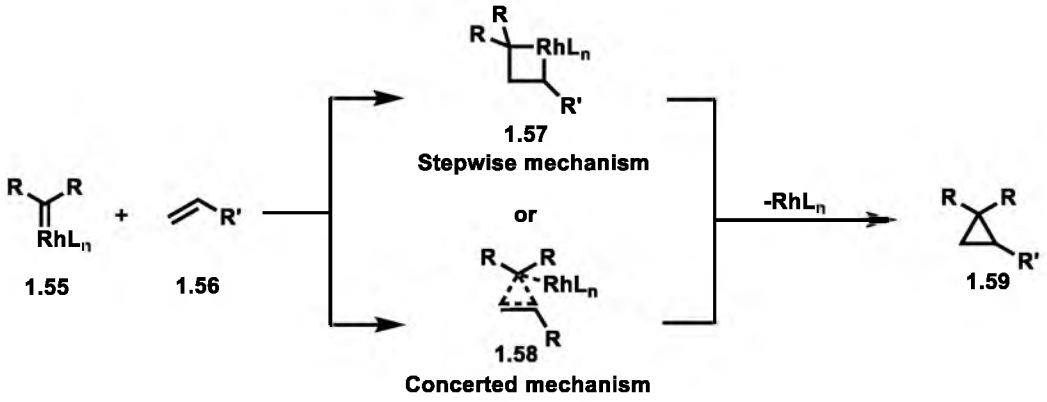
Scheme 1.11 Mechanism of X-H Insertion



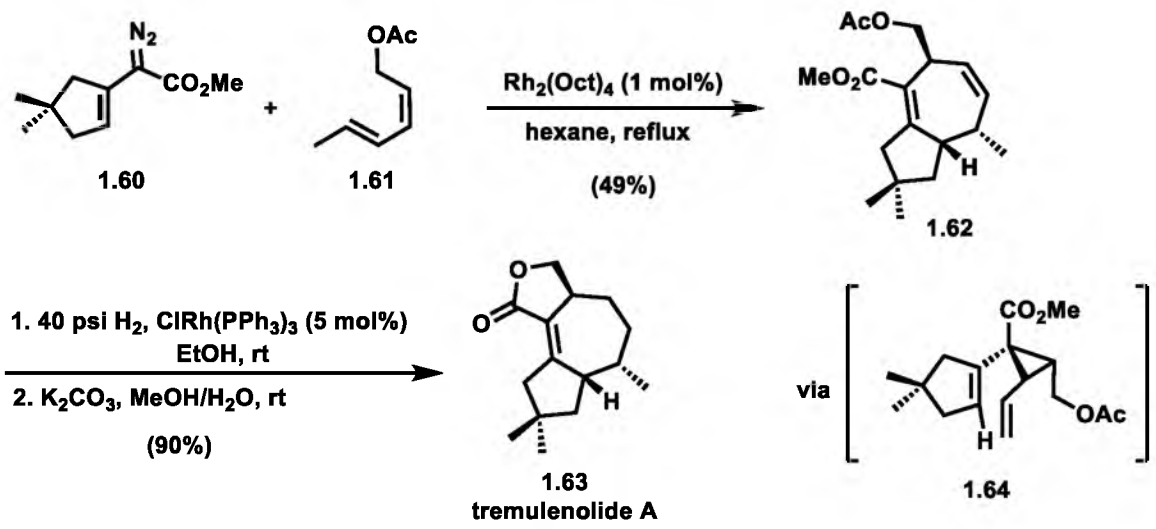
Scheme 1.12 Moody's total synthesis of siphonazole

It has been long recognized that metal carbenoids react with alkenes to provide cyclopropanes.[20] Both a concerted and a stepwise mechanism have been proposed (Scheme 1.13). The Davies group discovered that when an appropriate substrate was utilized, a subsequent Cope rearrangement could take place to form the cycloheptadiene. An elegant example came during their total synthesis of tremulenolide A (Scheme 1.14).[21] Diazo **1.60** reacted with the less sterically hindered *Z*-alkene in **1.61** in a stereoselective manner to give **1.64** first. A subsequent Cope rearrangement provided cycloheptadiene **1.62** as a single diastereomer. Hydrogenation and lactone formation led to tremulenolide A.

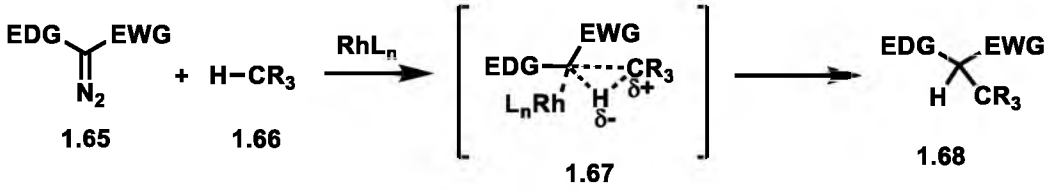
The Davies group first demonstrated that donor-acceptor metal carbenoids participated in intermolecular C-H insertions with high efficiency and selectivity.[22] The optimal catalysts usually were proline-based rhodium carboxylates such as $Rh_2(DOSP)_4$. Mechanistically, C-H insertion with Rh carbenoids is believed to occur in a concerted manner. The hydrogen approaches the carbenoid center causing partial positive charge build-up on the carbon of the C-H bond as indicated by **1.67** (Scheme 1.15).[23]



Scheme 1.13 Mechanism of cyclopropanation

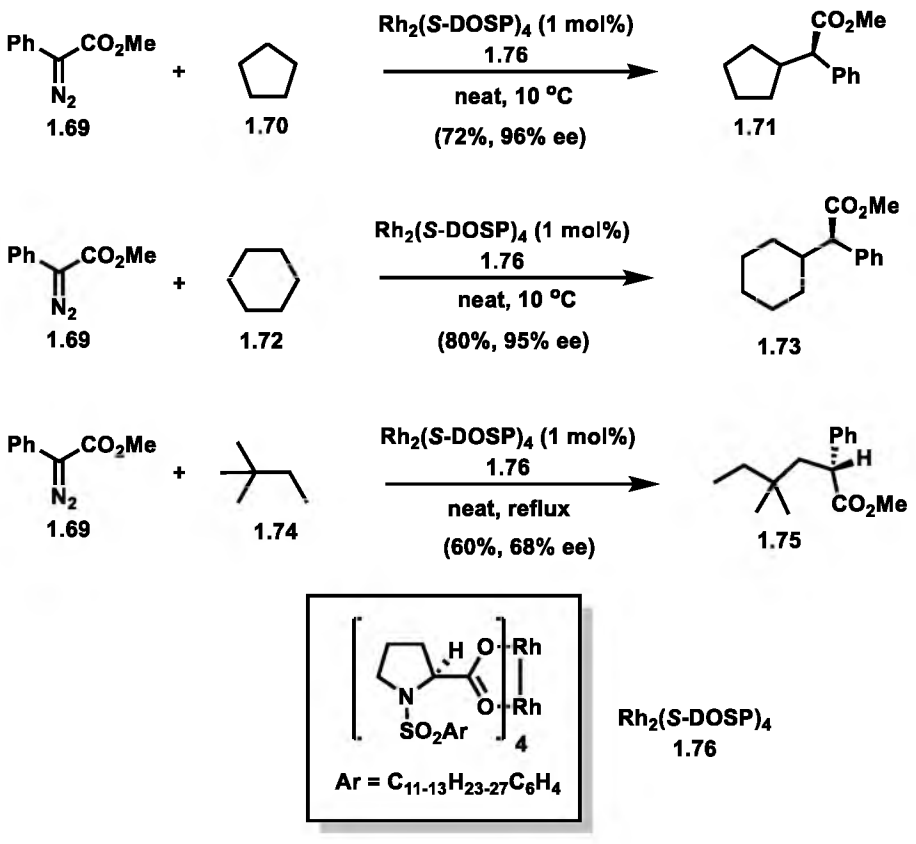


Scheme 1.14 Davies' total synthesis of tremulenolide A



Scheme 1.15 Mechanism of intermolecular C-H insertion

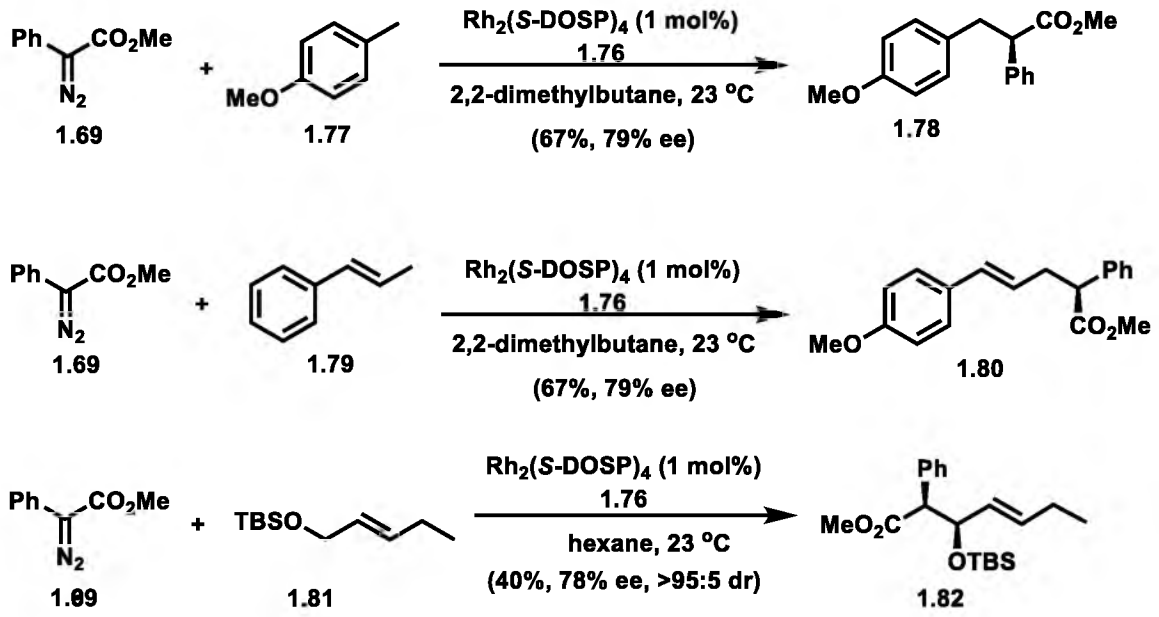
Due to their lower reactivity, when compared to traditional acceptor-acceptor type metal carbenoids, donor-acceptor metal carbenoids overcome the dimerization problem and are more selective towards insertions of different C-H bonds. For example, simple alkanes have been shown to participate in intermolecular C-H insertions with good chemo-, regio- and enantioselectivity (Scheme 1.16).[23] In general, secondary C-H bonds are the most reactive towards C-H insertions.[23] Cyclopentane **1.70** and cyclohexane **1.72** were very good substrates for C-H insertions as reactions completed at low temperatures.[24]



Scheme 1.16 C-H insertion of simple alkanes

In contrast, the C-H insertion of 2,2-dimethylbutane **1.74** took place preferably at the primary C-H bond and elevated temperatures had to be applied. Presumably, it is because of the steric bulkiness surrounding the secondary C-H bond.[24]

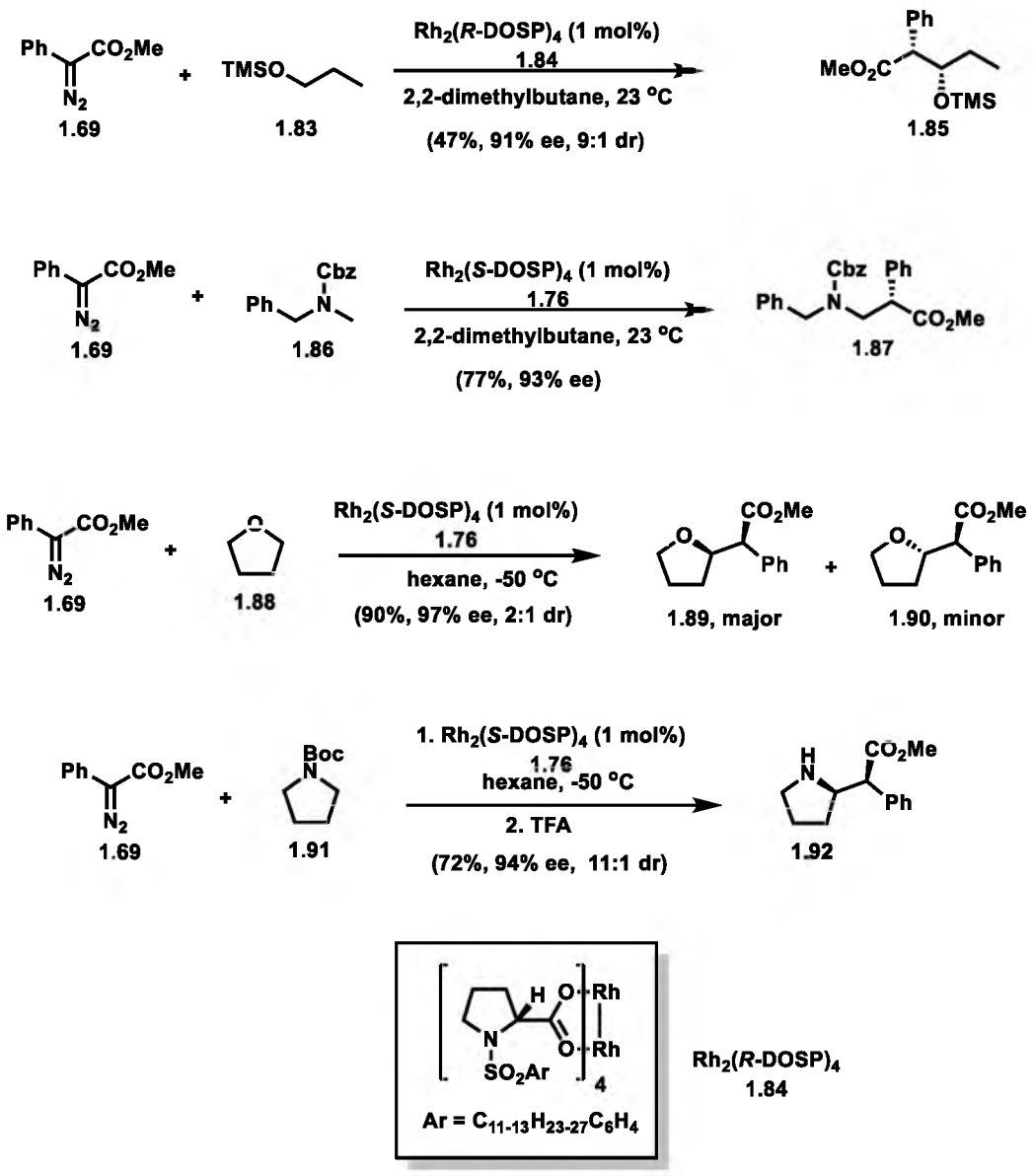
Allylic and benzylic C-H bonds are good substrates for intermolecular C-H insertions as the partial positive charge generated on the allylic or benzylic carbon can be efficiently stabilized by conjugation (Scheme 1.17).[25] Allyl silyl ethers such as **1.81** are even better substrates due to the additional stabilizing effect of the electron-rich siloxy group.[24] Compound **1.82** was isolated in excellent diastereoselectivity and good enantioselectivity when reacting **1.69** with **1.81** in the presence of $Rh_2(DOSP)_4$.



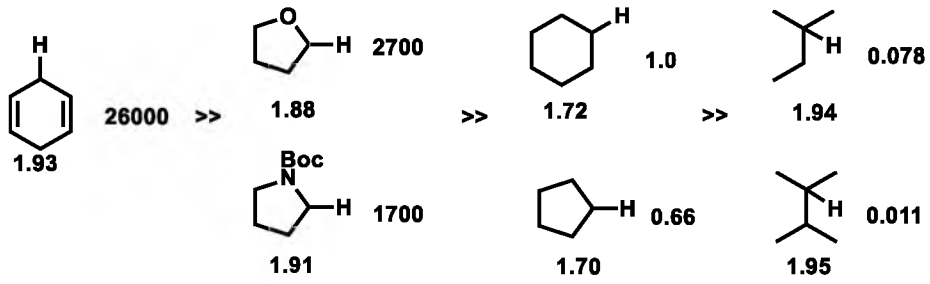
Scheme 1.17 C-H insertions into benzylic and allylic C-H bonds

Another type of C-H bond that is susceptible to the C-H insertion reaction is the C-H bond α to a heteroatom. Acyclic substrates such as amines and ethers reacted with aryl diazo esters in the presence of $Rh_2(DOSP)_4$ to provide C-H insertion products **1.85** and **1.87** with good diastereo- and enantiocontrol (Scheme 1.18).[24, 25b, 26] Interestingly, while insertion of the donor-acceptor metal carbenoid into Boc- protected pyrrolidine **1.91** proceeded with high diastereoselectivity, C-H insertion into the corresponding furan **1.88** only gave quite low diastereoselectivity.[24, 27]

A general reactivity trend has been established in order to understand the selectivity of intermolecular insertion into different C-H bonds (Scheme 1.19). The C-H insertion of 1,4-cyclohexadiene **1.93** was determined to be the fastest, followed by that of the C-H bond adjacent to a heteroatom. The reaction of simple alkanes was much slower.[24]



Scheme 1.18 C-H insertions into C-H bonds adjacent to heteroatoms

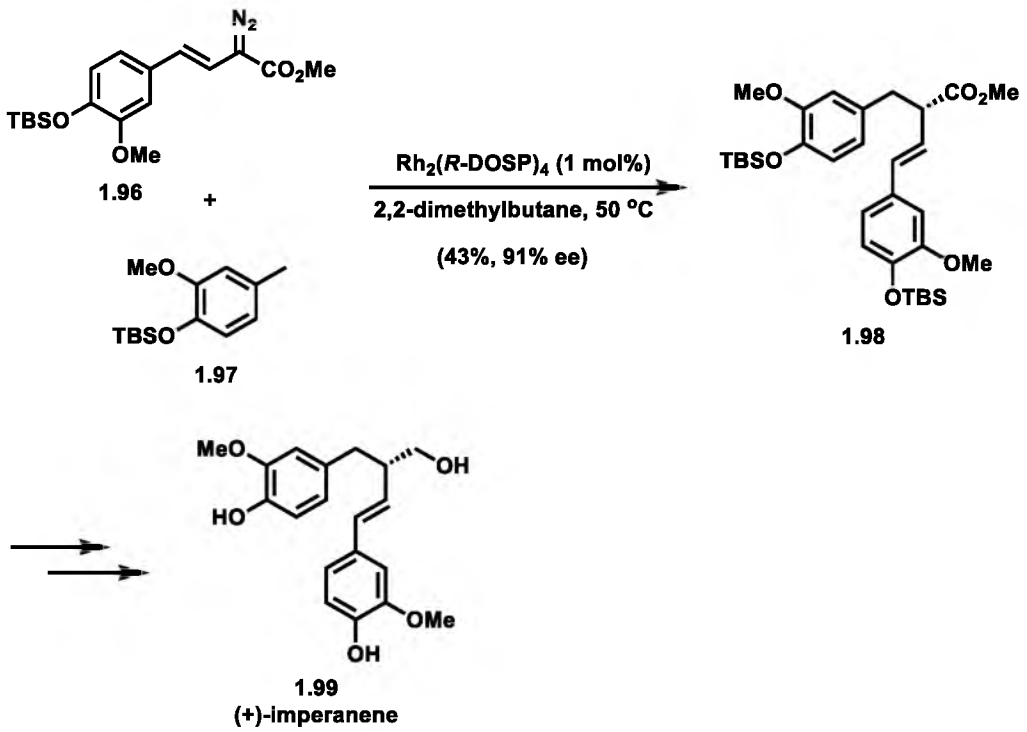


Scheme 1.19 Relative rates for C-H insertion of metal carbenoids

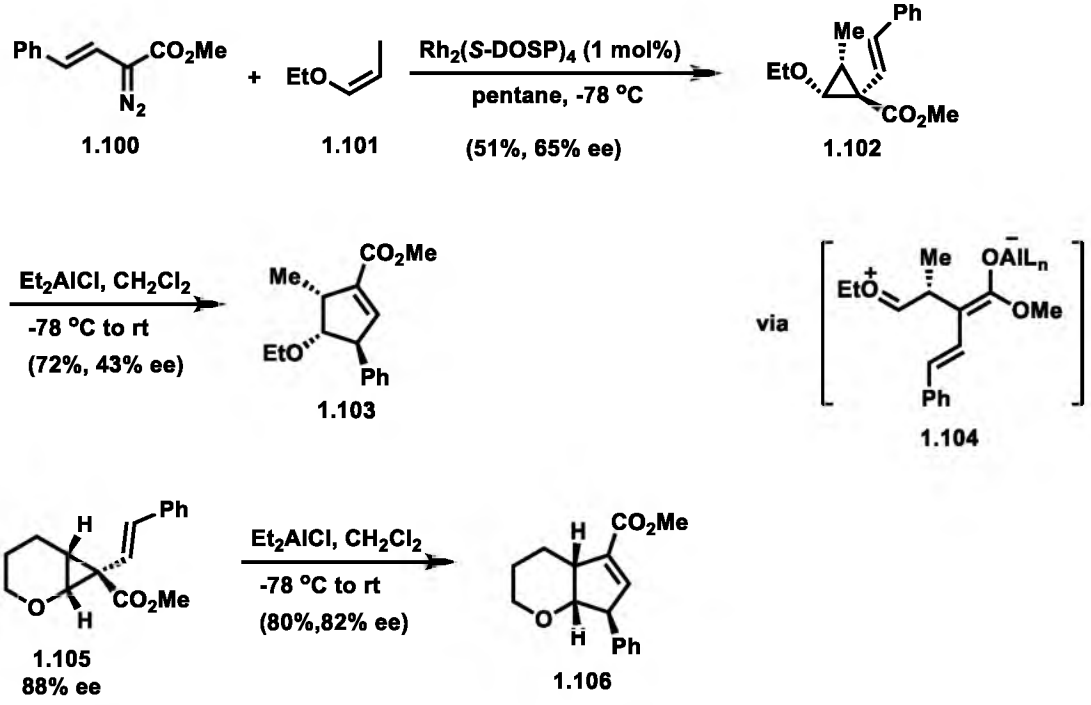
In the total synthesis of (+)-imperanene, the key step was an intermolecular C-H insertion of vinyl diazo acetate **1.96** with benzylic methyl group in substrate **1.97** (Scheme 1.20).[28] In the presence of Rh_2(*R*-DOSP)$_4$ this transformation produced the desired product **1.98** with 43% yield and 91% ee. Further functional group manipulations generated the natural product.

1.3 Vinyl metal carbenoids: versatile synthetic intermediates

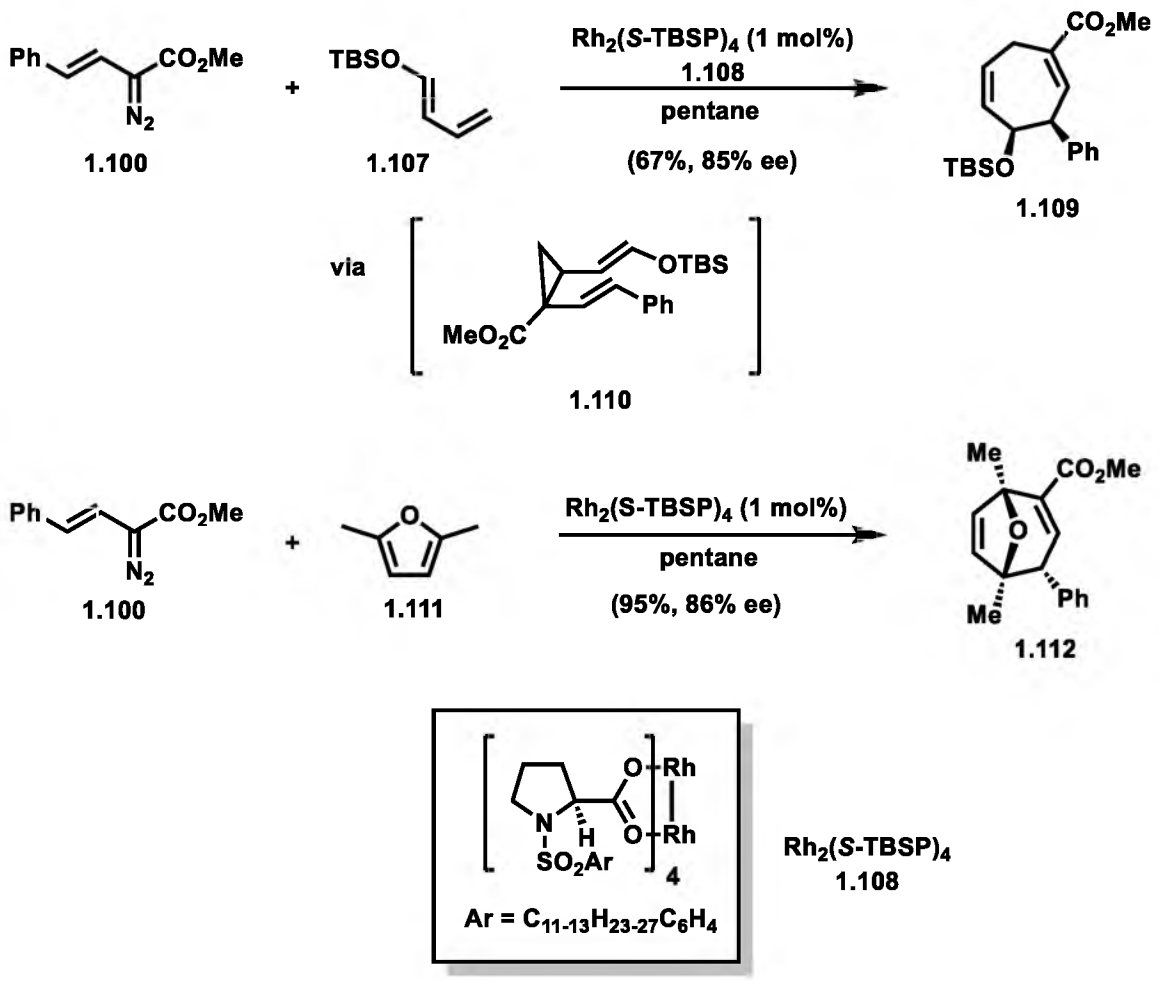
The vinyl metal carbenoid is a more versatile synthetic intermediate than the simple metal carbenoid because further transformations can be easily carried out on the vinyl group. In addition, vinyl metal carbenoids show unique vinylogous reactivity. It is well known that vinyl metal carbenoids undergo cyclopropanation and subsequent rearrangements resulting in formal [3+2] cycloadditions. As illustrated in Scheme 1.21, a stereoselective cyclopropanation between vinyl diazo ester **1.100** and vinyl ether **1.101** in the presence of Rh_2(DOSP)$_4$ gave cyclopropane **1.102**.[29] Treating **1.102** with Et_2AlCl rendered the cyclopentene **1.103** with some loss of optical purity. Interestingly, the optical purity was mostly retained when a more sophisticated substrate such as **1.105** was converted into **1.106**. On the other hand, [3+4] cycloaddition is highly stereoselective because both the cyclopropanation and subsequent Cope rearrangement take place in excellent stereocontrol (Scheme 1.22).[30] Notably, Cope rearrangement is believed to accomplish through a boat-like transition state as indicated in **1.110**. It's worth mentioning that cyclopropanation of diene **1.107** only happened on the terminal alkene due to the bulky siloxy group.



Scheme 1.20 Davies's total synthesis of (+)-imperanene

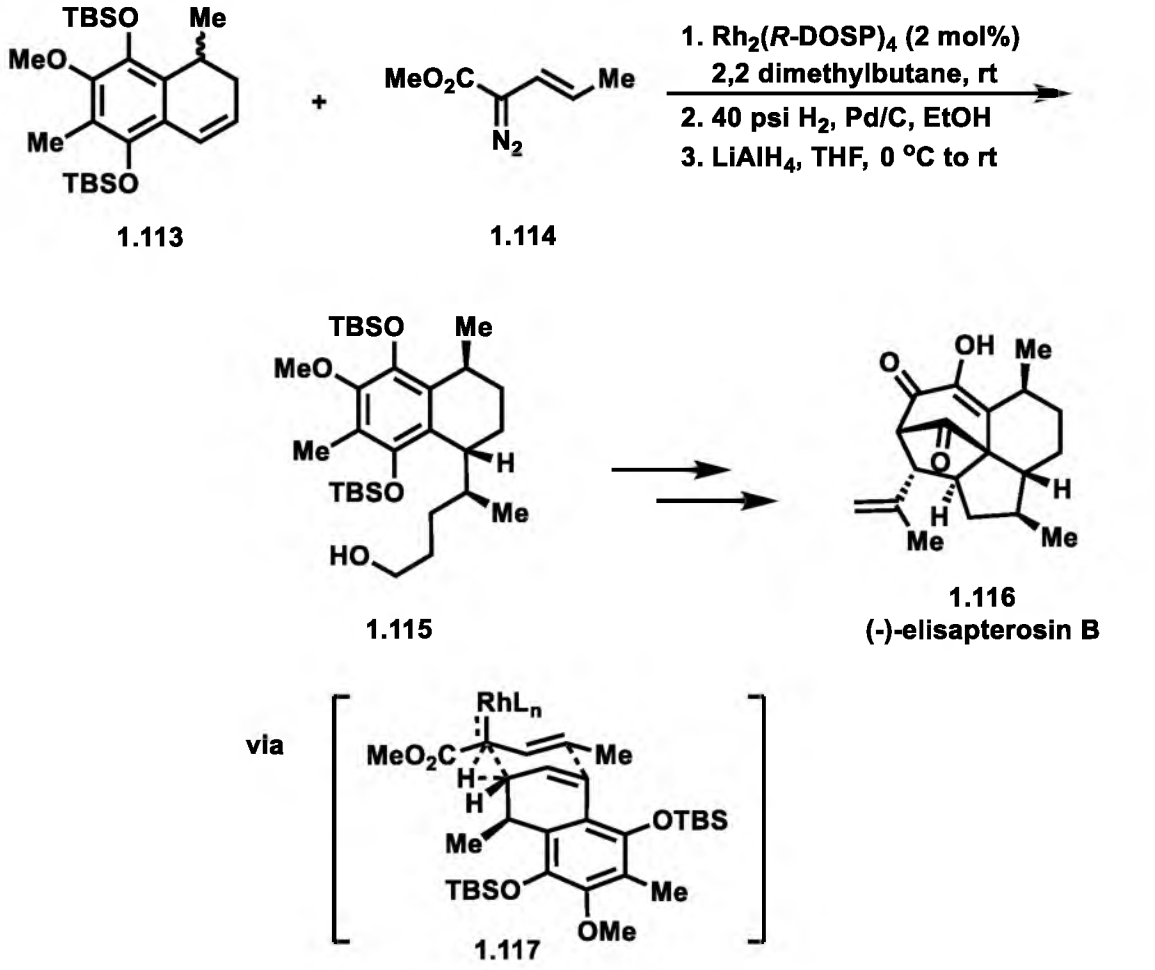


Scheme 1.21 [3+2] Annulation of vinyl carbenoids and vinyl ethers



Scheme 1.22 [3+4] Annulation of vinyl carbenoids and vinyl ethers

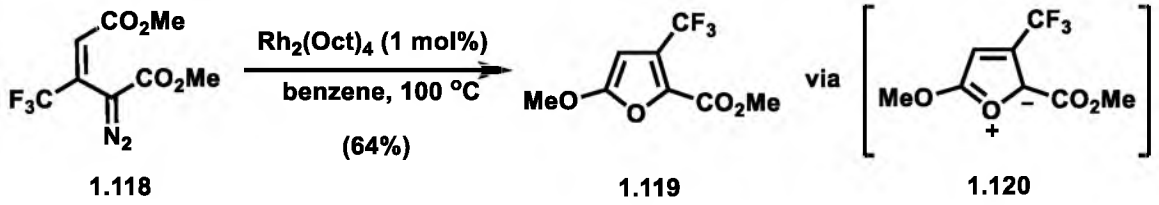
A very interesting reaction of vinyl metal carbenoids is the allylic C-H insertion-Cope rearrangement. The Davies group has extensively studied this reaction in an effort to expand the substrate scope and to illustrate the mechanism of this reaction. In the total synthesis of elisapterosin B, the Davies group have demonstrated that diazo ester **1.114** reacted with compound **1.113** enantio- and diastereoselectively. They believe a concerted allylic C-H activation/cope rearrangement mechanism is involved as illustrated by **1.117** (Scheme 1.23).[31] Compound **1.115** was generated after functional group



Scheme 1.23 Davies's total synthesis of (-)-elisapterosin B

manipulations and then served as an advanced intermediate towards the total synthesis of elisapterosin B.

The Nikolaev group reported that when *E*-vinyl diazo ester **1.118** was treated with $Rh_2(Oct)_4$, furan **1.119** was formed in 64% yield (Scheme 1.24).[32] Presumably, this reaction was completed through a cyclic oxonium ylide **1.120**. This methodology provided an alternative way towards the synthesis of highly substituted furans.



1.118 1.119 1.120

Scheme 1.24 Synthesis of furans from *E*-vinyl diazo ester

1.4 Conclusion

Metal carbenoid chemistry has become a powerful tool for natural product synthesis. Its unique reactivity profile receives more and more attention from the synthetic community including our group. In the next three chapters, our efforts in utilizing diazo phosphonates as useful synthetic intermediates will be illustrated.

1.5 References

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CHAPTER 2

VINYL DIAZO PHOSPHONATES AS PRECURSORS FOR INDOLINES AND CYCLOPENTENES

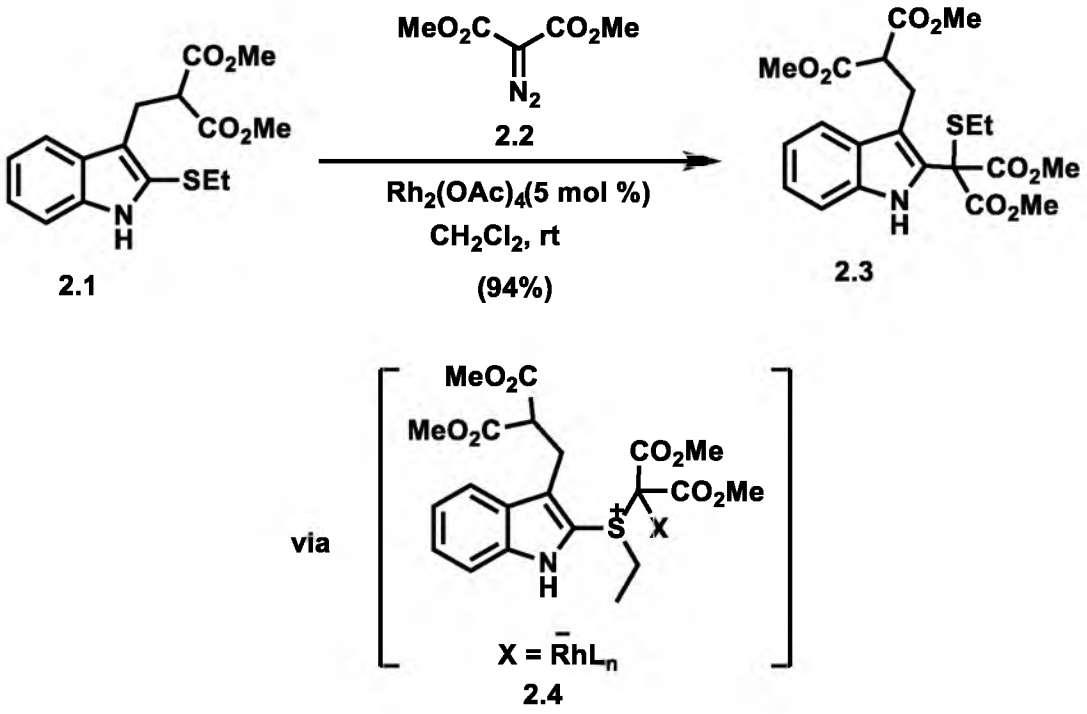
2.1 Vinyl diazo phosphonates as precursors for indolines

2.1.1 Introduction

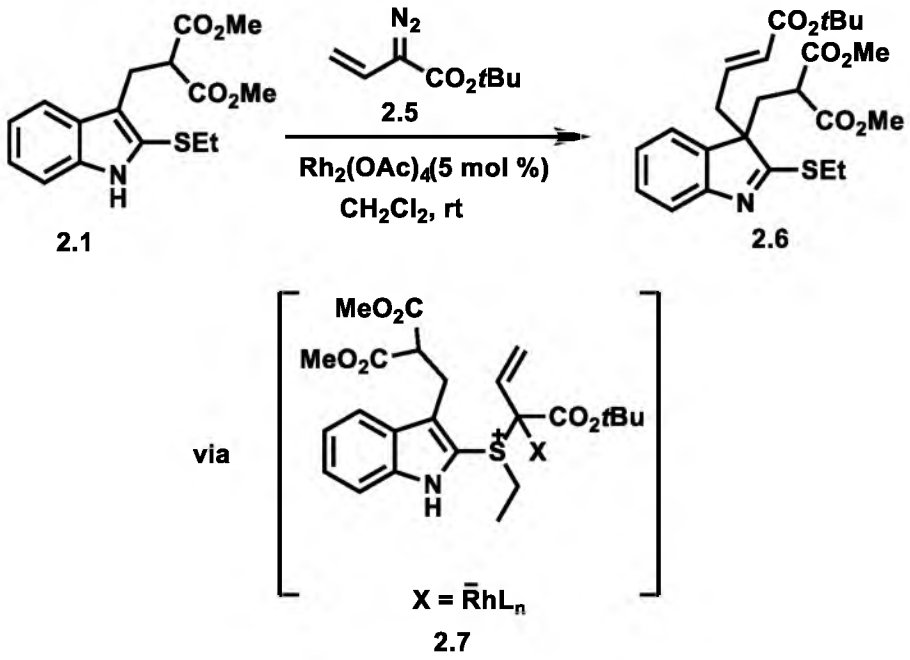
Indole natural products receive a significant amount of attention due to their prominent anti-bacterial, antifungal and anticancer activities.[1] Our group has been engaged in utilizing thioindoles as precursors for complex indole synthesis.

Notably, former group member Dr. Kennedy discovered that when treating 2-thioindole **2.1** with diazo ester **2.2**, a sulfur ylide **2.4** was formed first, which subsequently underwent a [1,2]-Stevens rearrangement to give insertion product **2.3** in 94% yield (Scheme 2.1).[2] In contrast, when vinyl diazo ester **2.5** was subjected to **2.1** under the same condition, a [3,3]-sigmatropic rearrangement occurred giving rise to C-3 quaternary-substituted indoline **2.6** (Scheme 2.2).

Former group member Dr. Novikov conducted an extensive study on this interesting rearrangement and demonstrated that the substrate scope was quite broad as shown in Table 2.1.[3] However, diastereoselectivities were quite low in all cases. The relative stereochemistry of the major isomer of **2.20** was assigned by X-ray crystallography (Scheme 2.3).

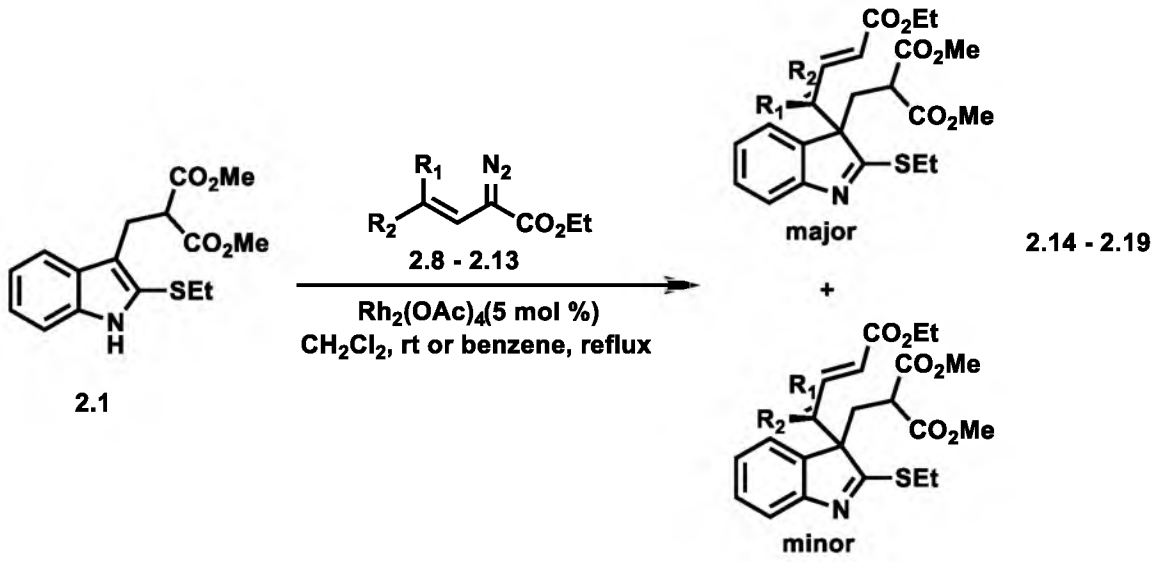


Scheme 2.1 Stevens rearrangement of 2-thioindole and diazo malonate

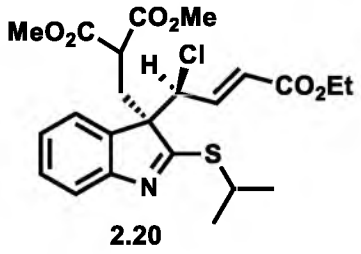


Scheme 2.2 [3,3] rearrangement of thioindoles and vinyl diazo esters

Table 2.1 [3,3]-Sigmatropic rearrangement: substrate scope



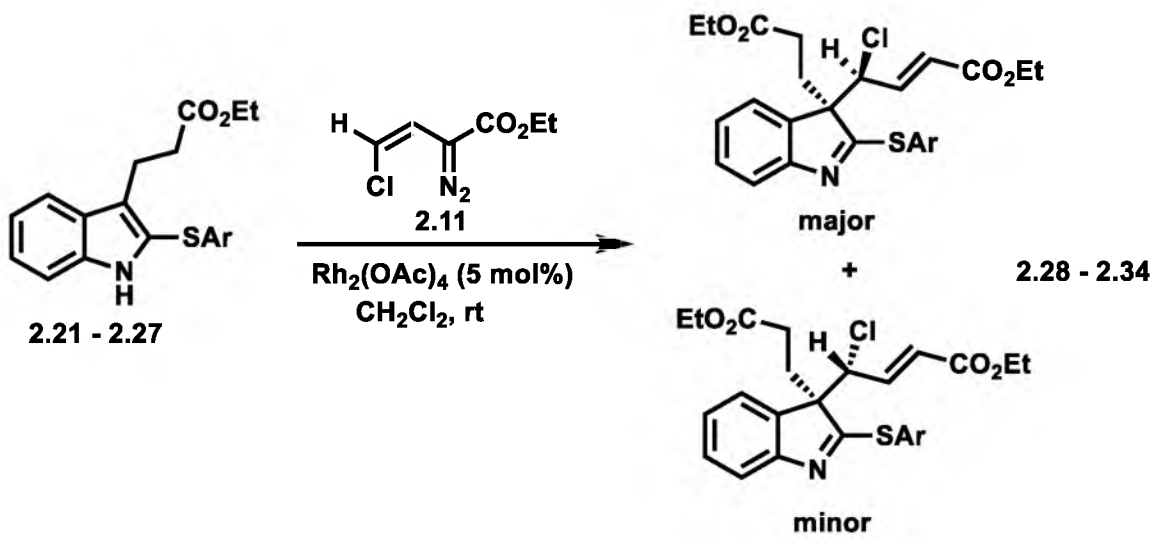
entry	diazo	R_1	R_2	product	d.r.	yield
1	**2.8**	H	Me	**2.14**	2:1	93%
2	**2.9**	H	CO_2Et	**2.15**	2:1	82%
3	**2.10**	H	Ph	**2.16**	1:1	95%
4	**2.11**	Cl	H	**2.17**	3:1	98%
5	**2.12**	Me	Me	**2.18**	n.a.	86%
6	**2.13**	Me	Ph	**2.19**	3:2	96%



Scheme 2.3 structure of major isomer 1.94 determined by X-ray

Former group member Dr. Boyarskikh investigated the effect of the substitutions on the thioindole for the [3,3]-sigmatropic rearrangement.[4] While he found the electronic environment of the arene groups had little effect on diastereoselectivity, enhancement was achieved when increasing the bulkiness of the arene group (Table 2.2). He also tested chiral rhodium catalysts for this transformation. Only moderate enantioselectivities were achieved.[5]

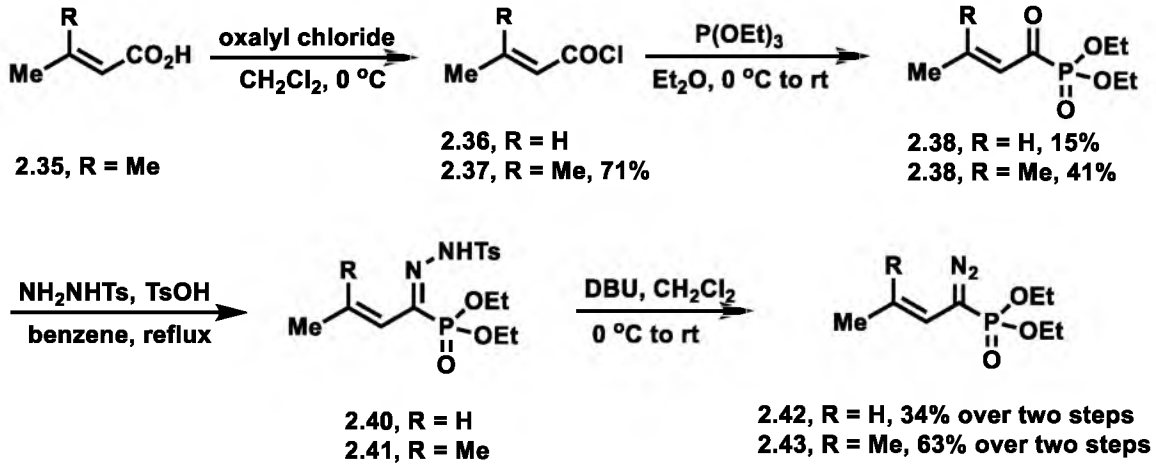
Table 2.2 Diastereoselectivity of [3,3]-sigmatropic rearrangement



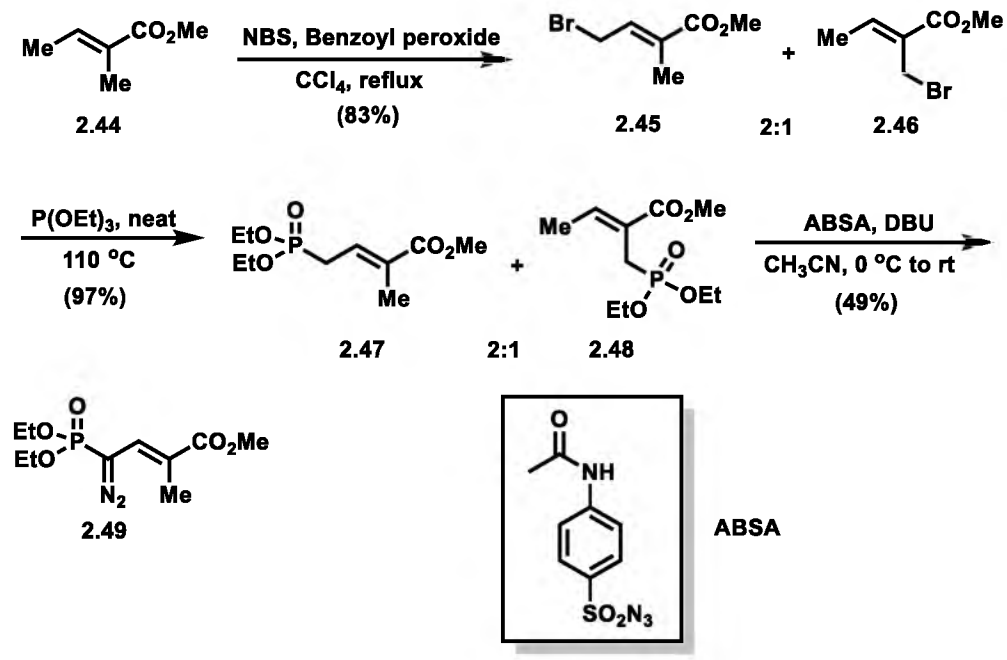
entry	Ar	d.r. (major/minor)	yield
1	Ph	7:1	82%
2	4-OMeC_6H_4	7:1	86%
3	4-$NO_2C_6H_4$	7:1	74%
4	2-FC_6H_4	7:1	74%
5	2-MeC_6H_4	11:1	75%
6	2,6-dimethylphenyl	15:1	96%
7	2-*i*PrC_6H_4	18:1	91%

In order to further expand the substrate scope of this rearrangement, Dr. Boyarskikh investigated vinylogous diazo systems other than diazo esters.[5] He turned his attention to diazo phosphonates due to the fact that phosphonates play an important role both in synthetic chemistry and biological systems. Two donor-acceptor type vinyl diazo phosphonates **2.42** and **2.43** were synthesized based on a known procedure which was then optimized by Dr. Boyarskikh (Scheme 2.4). The synthesis of acceptor-acceptor type vinyl diazo phosphonate **2.49** was also successful (Scheme 2.5).

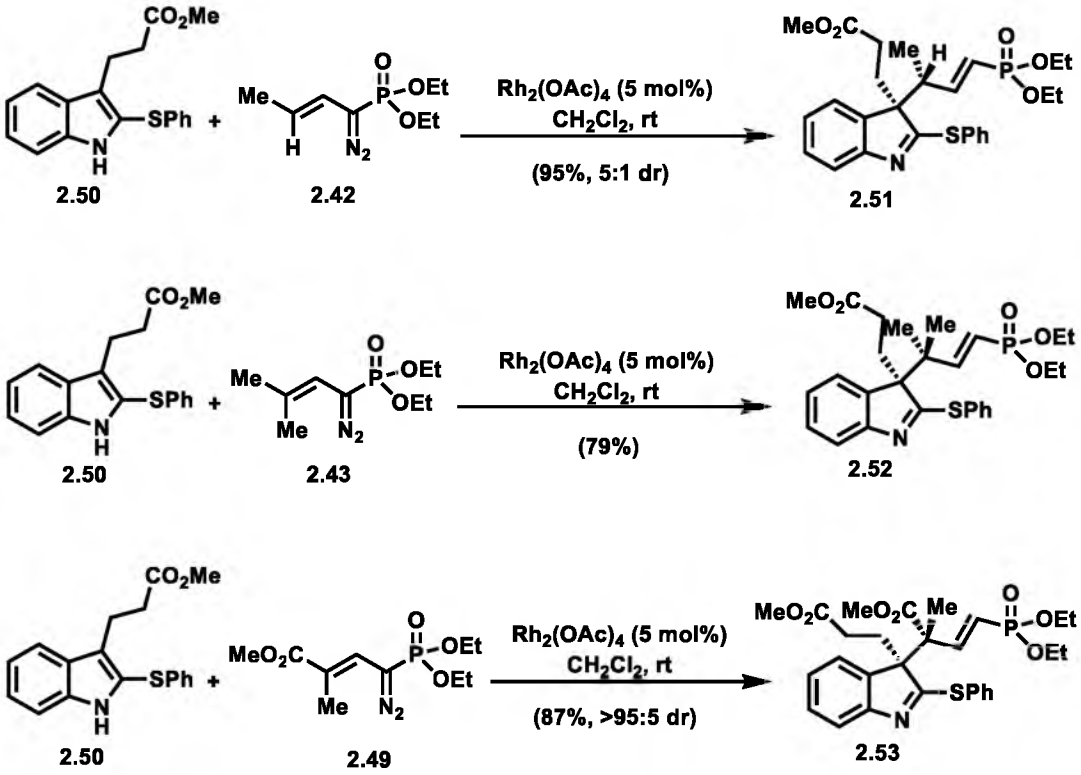
When treated with 2-thioindole **2.50**, the reaction of diazo phosphonate **2.42**, **2.43** and **2.49** gave the desired C-3 quaternary substituted indolines in good yield (Scheme 2.6).[5] Interestingly, the acceptor-acceptor type diazo phosphonate **2.49** showed a higher diastereoselectivity compared to the other donor-acceptor type diazo phosphonate **2.42**. Essentially, one single diastereomer of **2.53** was formed when **2.49** was treated with **2.50**.



Scheme 2.4 Synthesis of donor-acceptor vinyl diazo phosphonates



Scheme 2.5 Synthesis of acceptor-acceptor vinyl diazo phosphonate



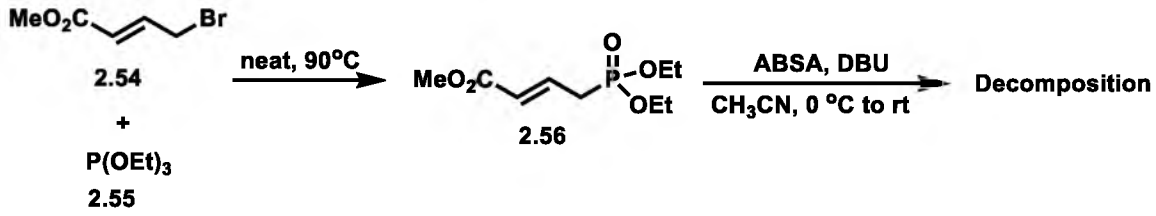
Scheme 2.6 [3,3]-Sigmatropic rearrangement of vinyl diazo phosphonates

2.1.2 Synthesis of indolines via a [3,3]-sigmatropic rearrangement

Although Dr. Boyarskikh was able to obtain several vinyl diazo phosphonates and successfully coupled them with 2-thioindoles, the lengthy and low-yielding procedure for synthesizing the diazo precursors greatly reduced their synthetic utility.

Preliminary data suggested that acceptor-acceptor type vinyl diazo phosphonate provided better diastereoselectivity when treated with 2-thioindoles in the presence of a rhodium catalyst. Encouraged by this result, we started to consider whether there was a better way to access the acceptor-acceptor type diazo phosphonates. It had been reported that phosphonocrotonate **2.56** could be made via an Arbuzov reaction by simply treating methyl bromocrotonate **2.54** with triethyl phosphite **2.55** (Scheme 2.7). Unfortunately, when treating compound **2.56** with ABSA and DBU, we were unable to isolate the desired diazo product.

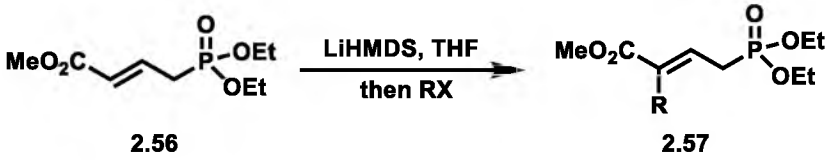
In 2002, the Marko group reported that a stereoselective monoalkylation of phosphonocrotonate **2.56** could be achieved by treating it with a base such as LiHMDS and an alkylating reagent (Scheme 2.8).[6] The alkylation happened solely at the position adjacent to the ester group. Only the *E*-isomer of the phosphonocrotonate product **2.57** was formed. Due to the fact that phosphonate **2.47** formed diazo phosphonate **2.49** successfully by a standard diazo transfer protocol, we believed that the alkylation would allow us to access a series of substituted phosphonocrotonates that could serve as precursors for diazo phosphonates.



Scheme 2.7 Synthesis of phosphonocrotonate and its diazo formation

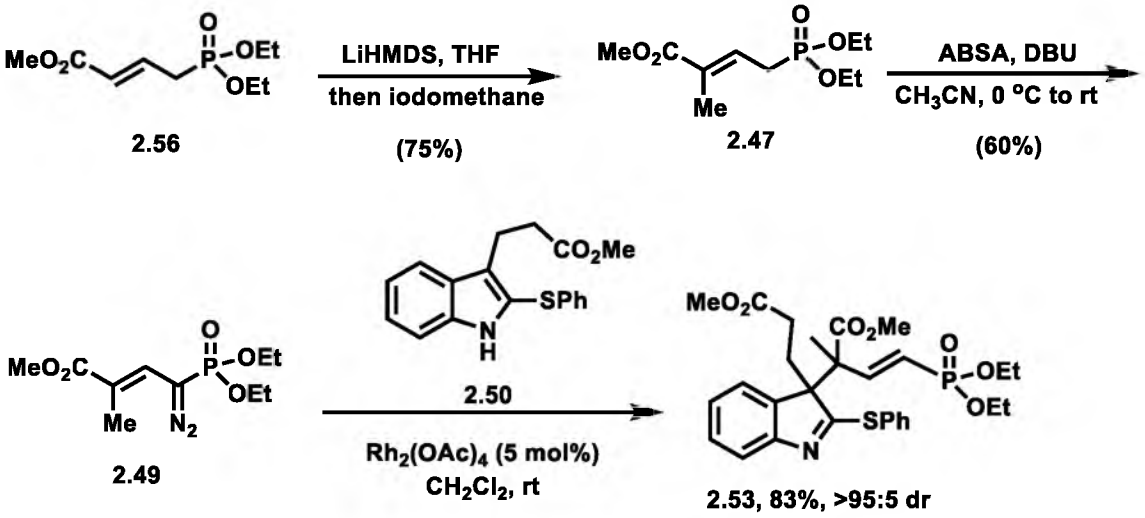
Gratifyingly, following the above-mentioned method, methyl substituted phosphonocrotonate **2.47** was synthesized in good yield (Scheme 2.9). Further structure elucidation proved that it was identical with the compound Dr. Boyarskikh had made using the previous method. Treating the substituted phosphonocrotonate with the standard diazo transfer condition using ABSA and DBU provided the desired diazo phosphonate **2.49** in 60% yield. When treated with thioindole, the desired C-3 quaternary indoline **2.53** was formed as a single diastereomer.

We were very excited about this result because it could provide a straightforward pathway towards the synthesis of indolines bearing a phosphonate group. So we decided to further explore the substrate scope of this transformation. Alkylation with iodoethane went smoothly to provide compound **2.58** although the yield was lower (Scheme 2.10). Diazo phosphonate **2.59** was formed following the previously described procedure. To our surprise, when treating the diazo **2.59** with 2-thioindole, a new product was formed in addition to the expected indoline product **2.60**. Careful NMR analysis revealed that the new compound was actually cyclopentene **2.61**.[7] Presumably, the cyclopentene **2.61** was formed via an intramolecular C-H insertion.



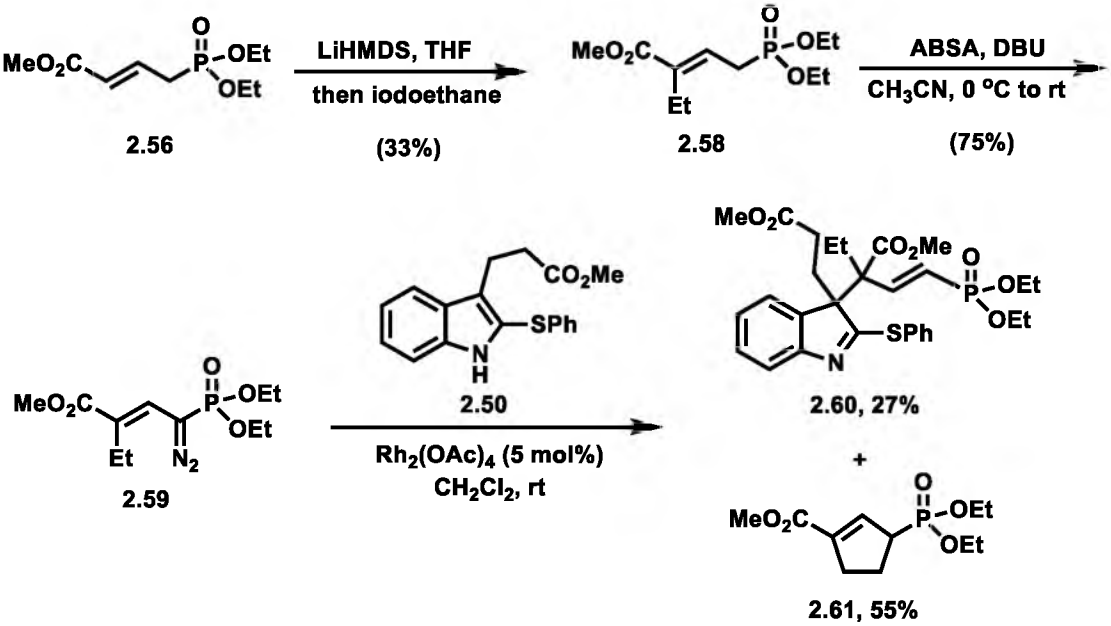
2.56 2.57

Scheme 2.8 Marko's stereoselective alkylation of phosphonocrotonate



2.56 2.47 2.49 2.53, 83%, >95:5 dr

Scheme 2.9 [3,3]-Sigmatropic rearrangement of vinyl diazo phosphonate



2.56 2.58 2.59 2.60, 27% 2.61, 55%

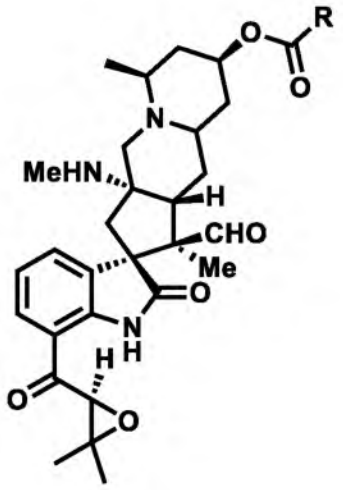
Scheme 2.10 Unexpected cyclopentene formation

2.1.3 Efforts towards the total synthesis of PF1270

Natural products bearing an oxoindole scaffold are widely prevalent in nature. We decided to target oxoindole natural products because they can be easily prepared from our C-3 quaternary substituted indolines. One family of natural products we were particularly interested in were PF1270 A, B and C, which were isolated in 2007 from culture broth of fungal strain PF1270 (Scheme 2.11).[8] In preliminary studies they displayed high affinity towards the rat histamine H3 receptors (K*i* 0.058, 0.17 and 0.19 mM, respectively) and human Histamine H3 receptors (K*i* 0.047, 0.12 and 0.22 mM, respectively).

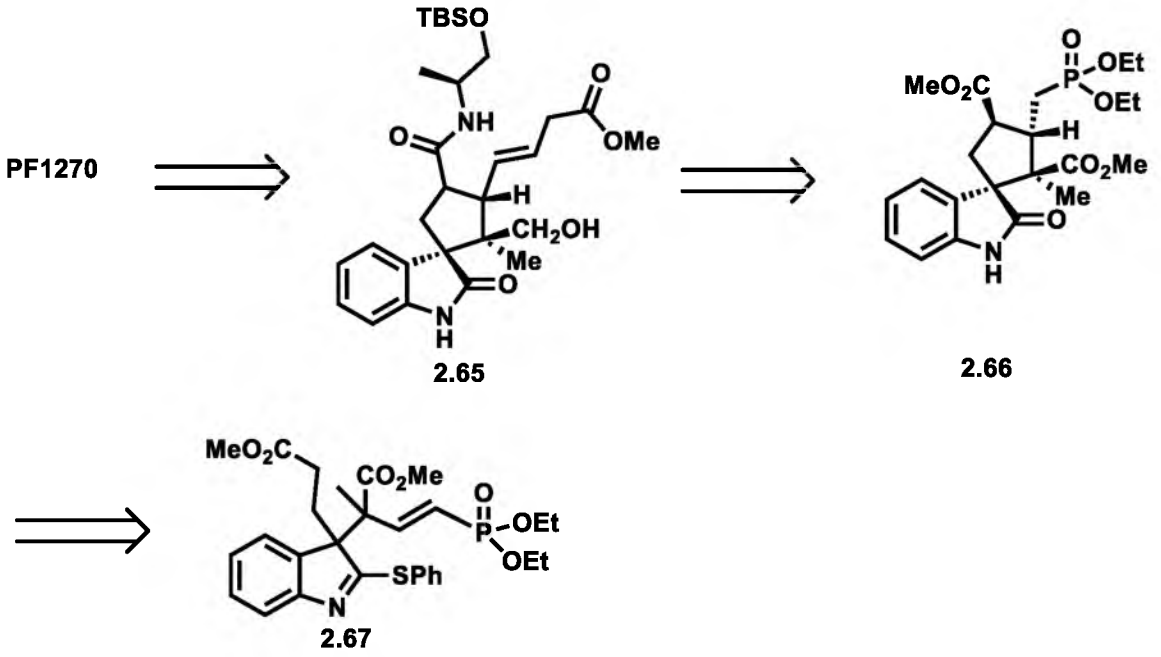
Retrosynthetically, PF 1270 can be synthesized from amide **2.65**, which is derived from phosphonate **2.66** via a Horner-Emmons reaction and functional group manipulation (Scheme 2.12). The cyclopentane ring in **2.66** would be formed by an intramolecular Michael addition of the α-carbon of the ester group to the vinyl phosphonate in compound **2.67**.

Preliminary results towards the intramolecular Michael addition were encouraging. Dr. Boyarskikh had demonstrated that a related cyclization was viable by treating α,β-unsaturated ester **2.68** with *t*-BuOK (Scheme 2.13).[5] However, attempts to facilitate the cyclization of vinyl phosphonate **2.70** to directly form **2.71** was unsuccessful (Scheme 2.14). Instead, Dr. Boyaskikh discovered that a cyclic phosphonate **2.72** was formed when treating **2.52** with LDA and TMSCl. Corresponding alcohol **2.73** could be formed by acidic hydrolysis. However, we were not able to convert either **2.72** or **2.73** to the desired natural product skeleton.

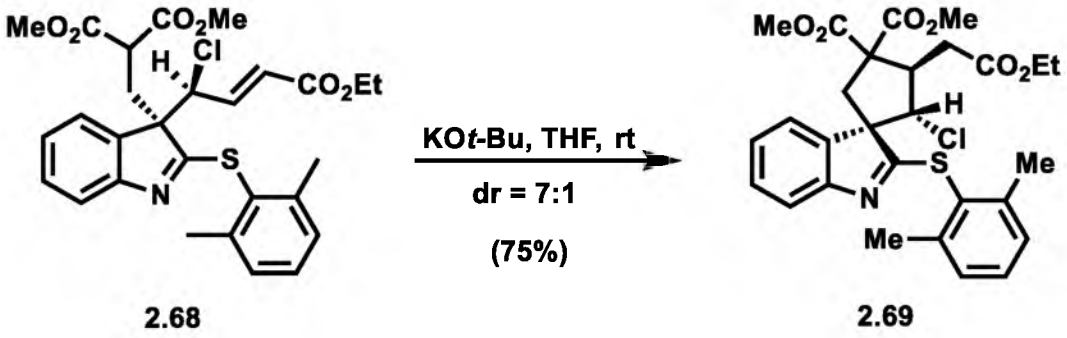


2.62, PF1270A, R = *n*-Pr
2.63, PF1270B, R = Et
2.64, PF1270C, R = Me

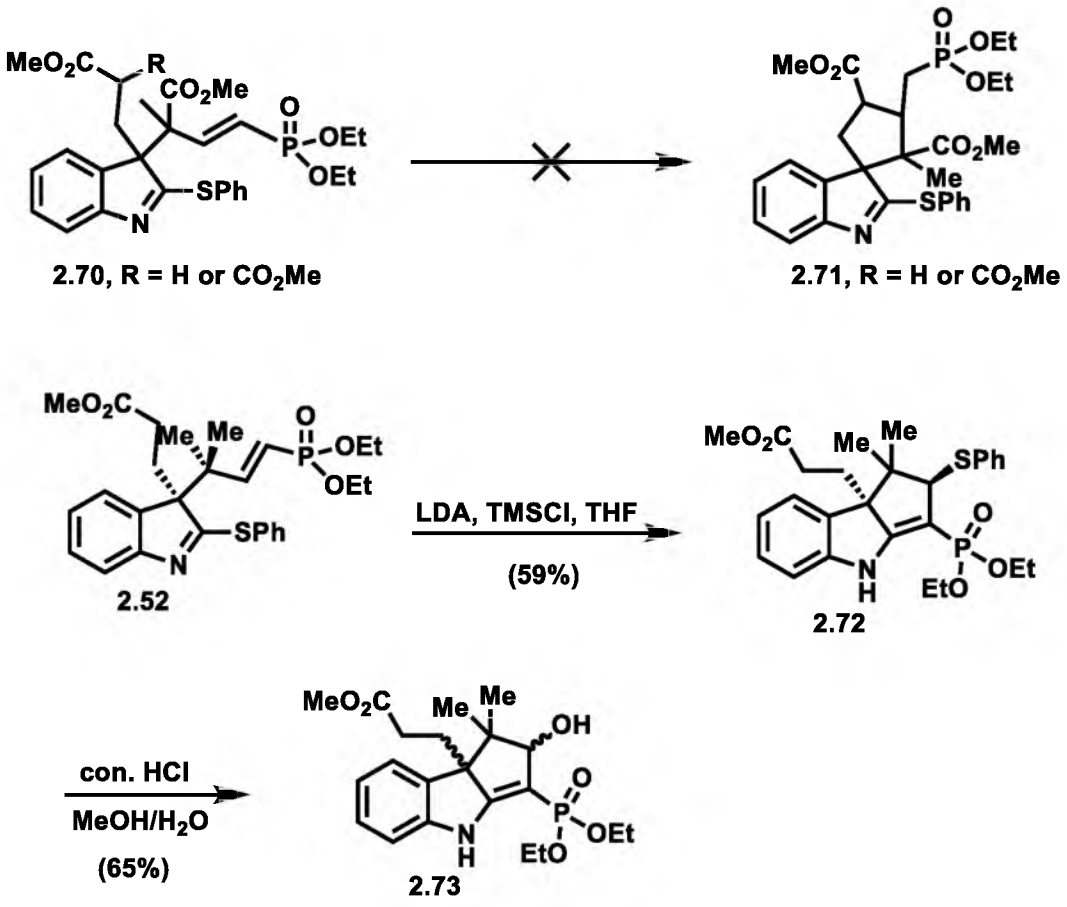
Scheme 2.11 Structure of PF1270 A, B and C



Scheme 2.12 Retrosynthetic Analysis of PF1270



Scheme 2.13 Successful Michael addition of unsatuated ester

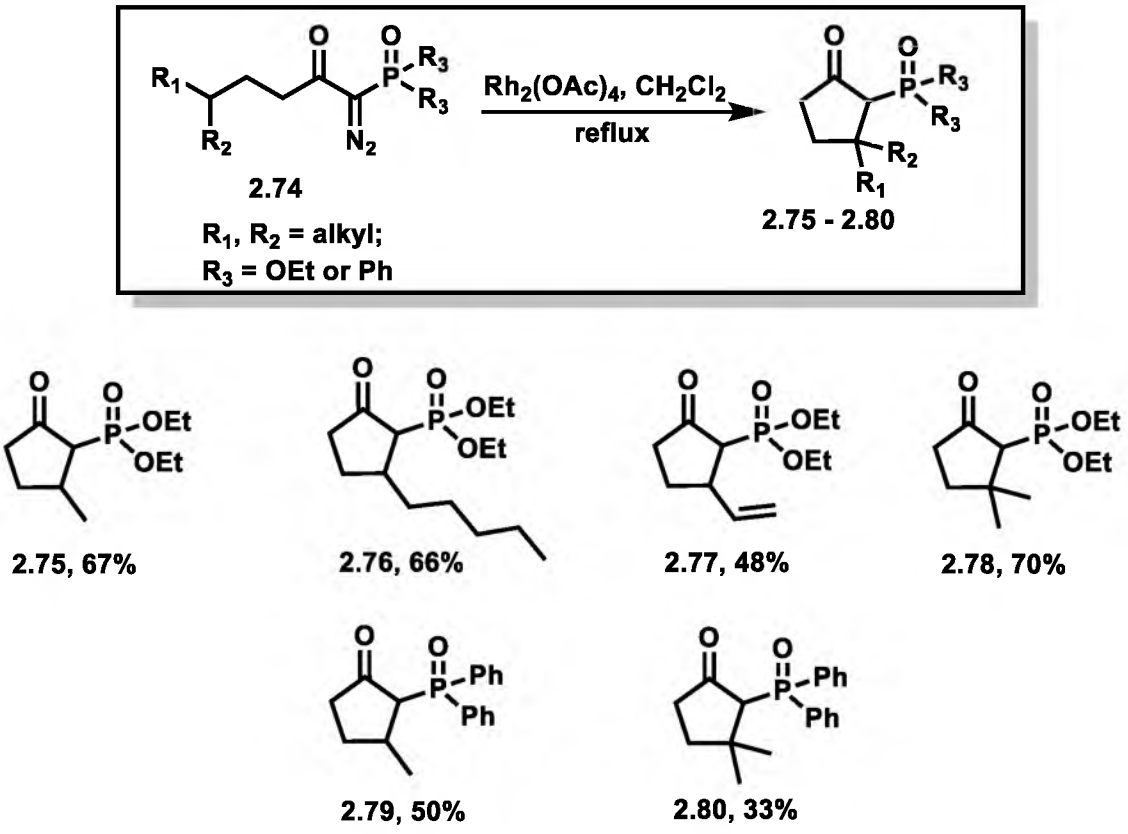


Scheme 2.14 Unsuccessful Michael addition of vinyl phosphonates

2.2 Vinyl diazo phosphonates as precursors for cyclopentenes

2.2.1 Introduction

Although intramolecular C-H insertions of diazo carbonyl compounds to form cyclopentanes are well known, reports of its diazo phosphonate counterpart have been rare and limited to α-diazo β-ketophosphonates. A good example was reported by Corbel et al as a series of α-diazo β-ketophosphonates or α-diazo β-ketophosphine oxides were treated with rhodium acetate and rendered the formation of phosphoryl cyclopentanones in moderate yield (Scheme 2.15).[9] To the best of our knowledge intramolecular C-H insertion of vinyl diazo phosphonates or esters has not yet been reported.

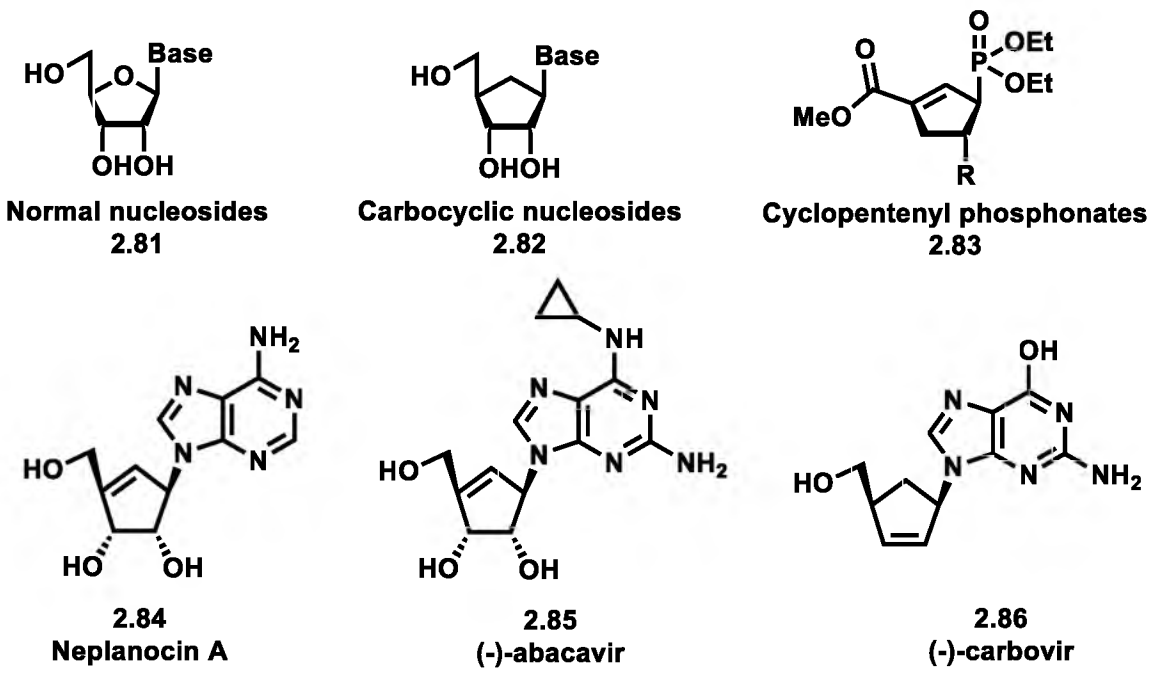


Scheme 2.15 Intramolecular C-H insertion of diazo ketophosphonates

We came to believe that the synthetically unique transformations of vinyl diazo phosphonates mentioned above can be useful for the construction of bio-active molecules. Of particular interest were the newly formed cyclopentenyl phosphonates which resemble carbocyclic nucleosides.[10] Carbocyclic nucleosides are nucleoside analogues that have attracted interest from medicinal chemists due to their applications as anti-viral, anti-HIV and anticancer agents.[10] Their structural similarities to nucleosides provide the hope that they are likely to bind to the same protein targets, while the lack of a glycosidic linkage increases their stability against enzymatic degradation. Cyclopentane type carbocyclic nucleosides are found both in nature and synthesized artificially. A few interesting carbocyclic nucleosides are shown in Scheme 2.16. Neplanocin A is a naturally occurring carbocyclic nucleoside that has shown significant antitumor activity against L1102 Leukemia in mice.[11] (-)-Carbovir was discovered as early as 1989 and demonstrated anti-HIV activity.[12] (-)-Abacavir exhibited even stronger anti-HIV activity and is the major effective component in the FDA approved drug Ziagen.[13]

2.2.2 Synthesis of cyclopentenes via an intramolecular C-H insertion

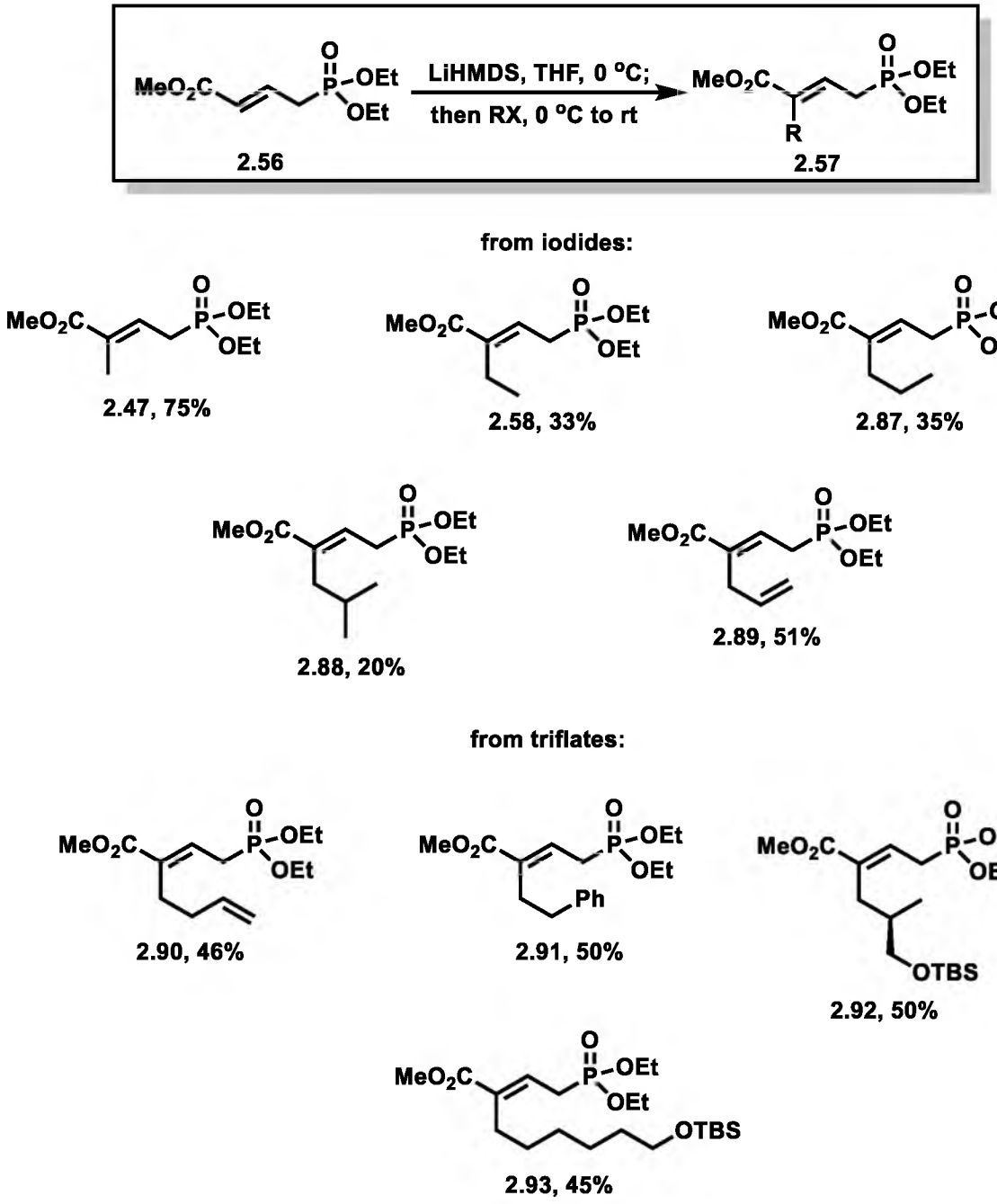
Interested in the potential synthetic utility of cyclopentenyl phosphonates, we decided to expand the substrate scope of this methodology. Alkylation with primary iodides or triflates provided the desired mono-substituted phosphonates (Scheme 2.17). The relatively low yields for some iodides were mainly due to dialkylation and decomposition of the phosphonocrotonate precursor **2.56**.



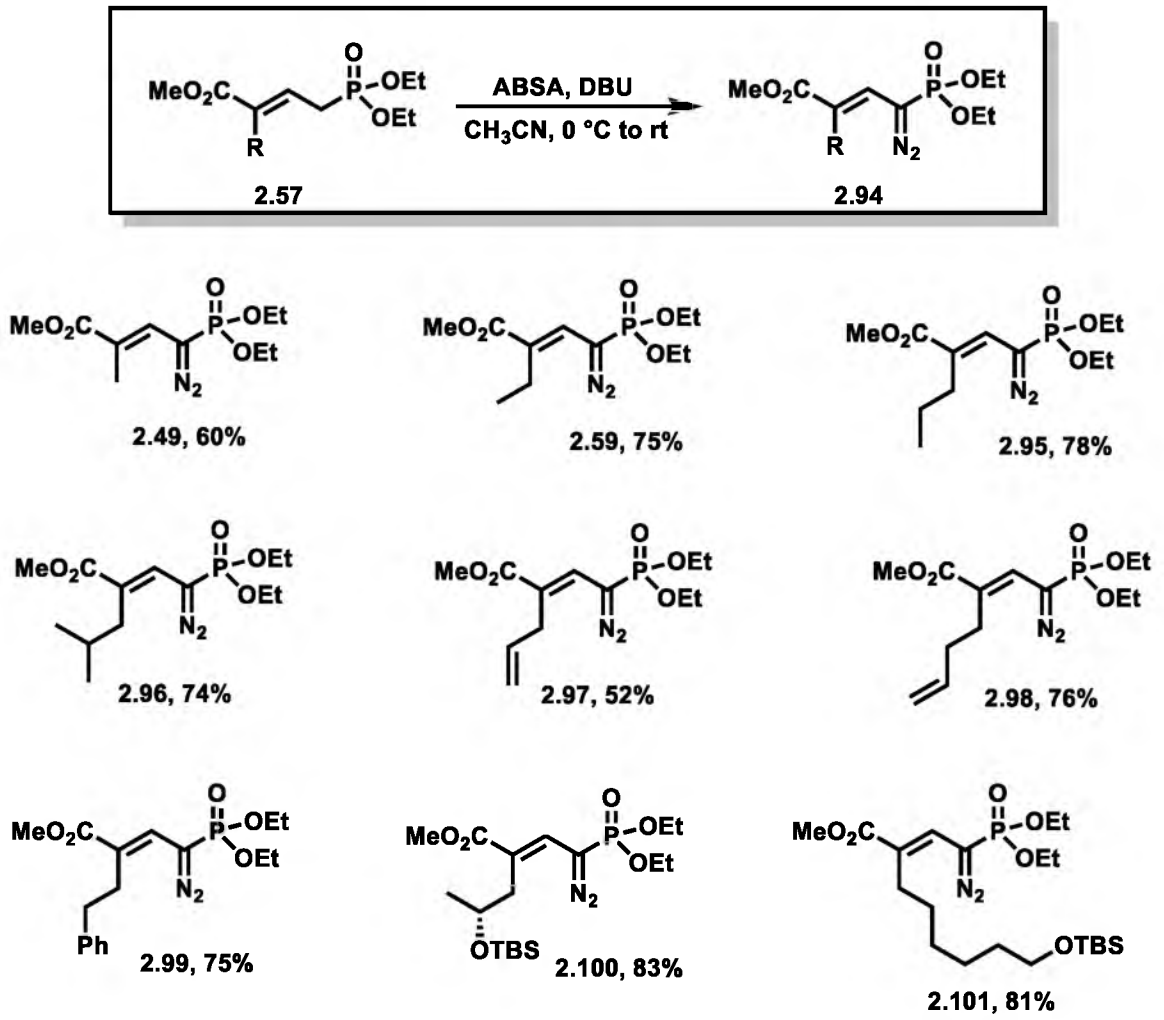
Scheme 2.16 Structure of carbocyclic nucleosides

Triflates should be the preferred alkylating reagents because first, triflates normally gave higher yield than the corresponding iodides; second, simple alcohol precursors for making triflates are commercially available. It is also noteworthy to mention that in both Marko and our experiments, alkylations occurred in a regio- and stereocontrolled manner as the alkylations happened solely on the α-carbon of the ester and the resulting α,β-unsaturated esters were isolated exclusively as the *E* alkenes.

Diazo transfer of the substituted phosphonates went uneventfully to provide the corresponding diazo phosphonates in good yield (Scheme 2.18). The configurations of the alkenes were determined to be *E*-isomers Based on NOE experiments.

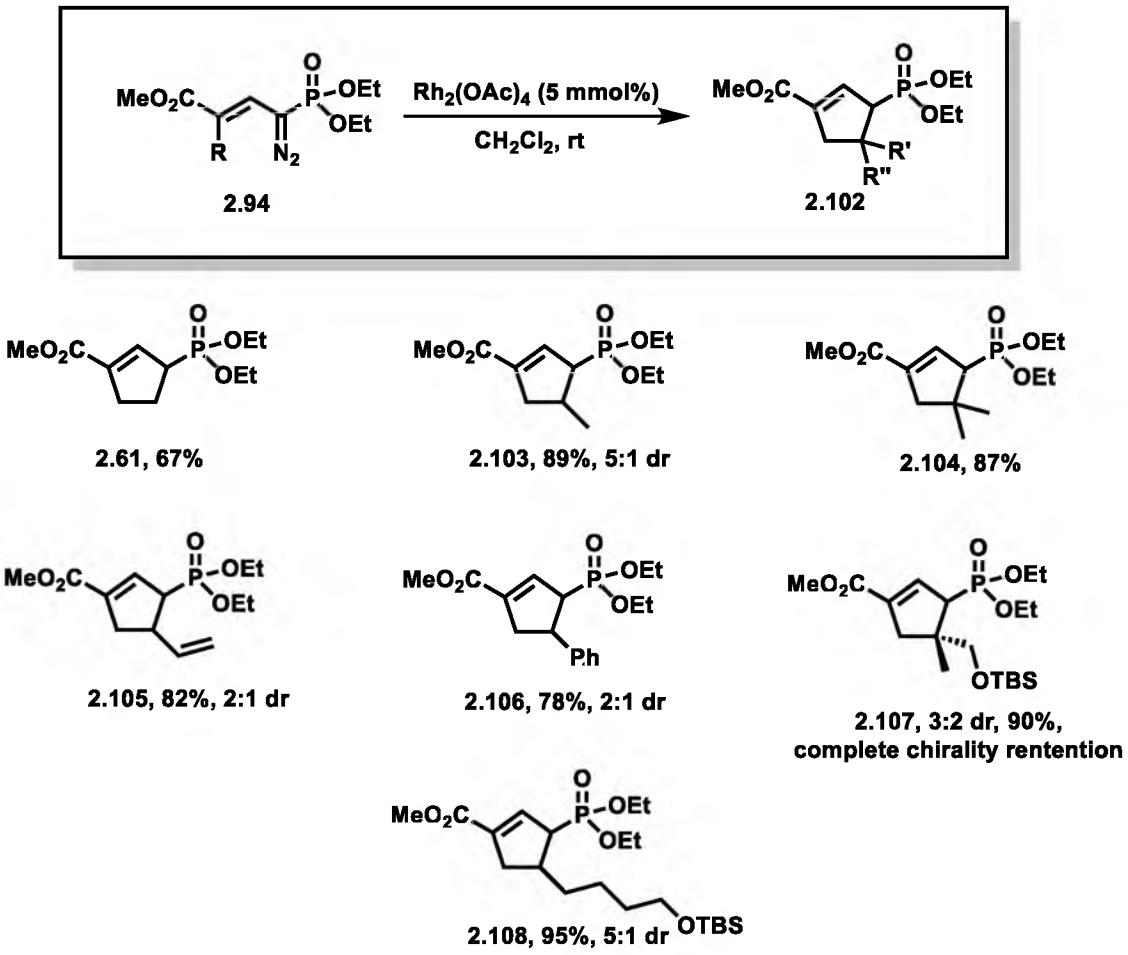


Scheme 2.17 Alkylation of phosphonocrotonates: substrate scope



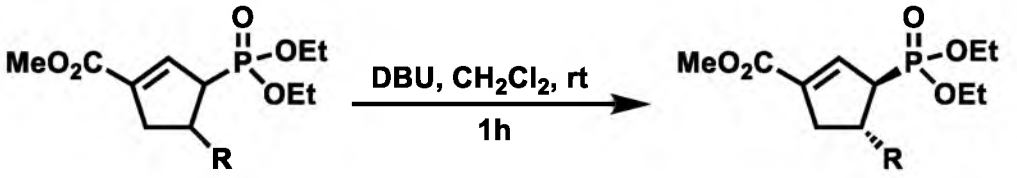
Scheme 2.18 Formation of vinyl diazo phosphonates: substrate scope

With the diazo phosphonates in hand, intramolecular C-H insertions were performed in the presence of $Rh_2(OAc)_4$. To our delight, the desired cyclopentenes were the only isolated products in high yield (Scheme 2.19). Primary, secondary and tertiary C-H bonds were all suitable substrates for the C-H insertion reactions. Diastereoselectivity of the secondary C-H insertion was generally moderate. However, the thermodynamically more stable *trans*- isomer could be obtained by treating the mixture of diastereomers with DBU in CH_2Cl_2



Scheme 2.19 C-H insertion of vinyl diazo phosphonate: substrate scope

for 1h (Scheme 2.20). When an optically pure diazo phosphonate **2.100** was used in the reaction, the cyclopentene was formed as a 3:2 mixture of two diastereomers. We were pleased to find out that the absolute stereochemistry of the diazo phosphonate was completely transferred to the product as shown by chiral HPLC. Based on Taber's work, we believe that the absolute stereochemistry of the diazo **2.100** was retained in the reaction.[14] These findings demonstrate that this methodology can serve as a useful tool for diastereo- and enantio-selective synthesis of highly substituted cyclopentenes.



2.103, R = Me, 5:1 dr
2.105, R = vinyl, 2:1 dr
2.106, R = Ph, 2:1 dr

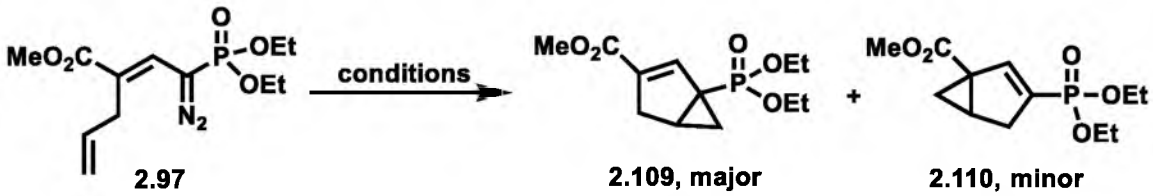
2.103, R = Me, >95:5 dr
2.105, R = vinyl, >95:5 dr
2.106, R = Ph, >95:5 dr

Scheme 2.20 Equilibration to trans phosphonates

Another rather unique substrate was diazo phosphonate **2.97** having an allyl group pendant to the diazo functionality. When treated with $Rh_2(OAc)_4$ **2.97** readily participated in the cyclopropanation reaction and gave the bicycle [3.1.0] substrates **2.109** and **2.110** (Table 2.3). Presumably, the minor product **2.110** was formed either through a [3+2] cycloaddition or isomerization of compound **2.109**.

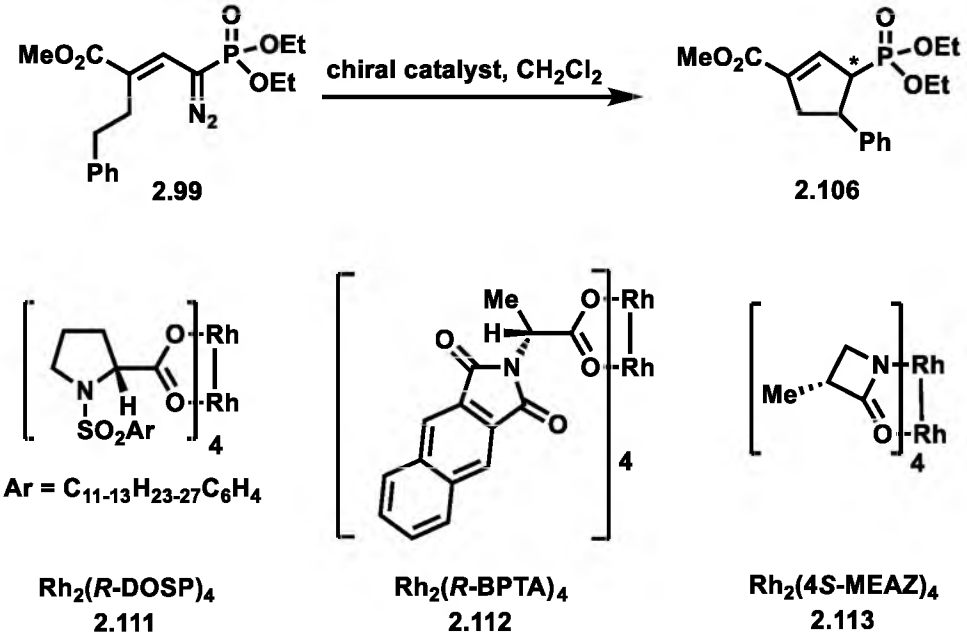
Asymmetric C-H insertion reactions have also been examined. Unfortunately, treating vinyl diazo phosphonates **2.99** with a number of chiral dirhodium catalysts including Rh_2(*R*-DOSP)$_4$, Rh_2(*R*-BPTA)$_4$, and Rh_2(4*S*-MEAZ)$_4$ resulted in minimal enantioselectivity, although the yield was comparable with achiral dirhodium catalyst such as $Rh(OAc)_2$ (Scheme 2.21). Given the fact that the [3,3]-sigmatropic rearrangement between 2-thioindole and vinyl diazo phosphonate also provided very low enantioselectivity when chiral dirhodium catalyst was applied, we believed that the chiral ligand on the dirhodium catalyst was too far-away from the diazo carbon resulting in unsatisfactory control of its stereochemistry.

Table 2.3 Cyclopropanation of vinyl diazo phosphonate



entry	catalyst	solvent	temp.	time	yield	major: minor[a]
1	$Rh_2(OAc)_4$	CH_2Cl_2	rt	2d	79%	4:1
2	$Rh_2(OAc)_4$	benzene	80 °C	4h	80%	6:1
3	$Rh_2(OAc)_4$	toluene	110 °C	2h	80%	10:1
4	$Rh_2(O_2CCF_3)_4$	CH_2Cl_2	rt	12h	81%	5:1
5	none	benzene	80°C	8h	64%	> 95:5
6	BINOL	CH_2Cl_2	rt	2d	55%	> 95:5
7	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	rt	10 min	93%	>95:5

[a] Ratio of diastereomers determined by the integrations of the vinyl proton peak in the ^1H NMR spectra of the crude reaction mixture.



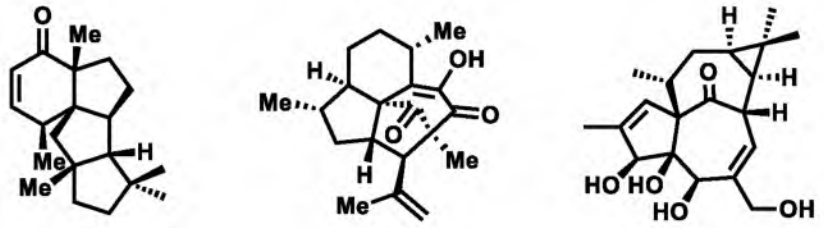
Scheme 2.21 Chiral catalyst for intramolecular C-H insertion

2.2.3 Synthesis of spiro bicyclic carbocycles

The high efficiency and specificity of cyclopentene ring formation suggest to us that this methodology can be applied to the construction of more complex structures. Since insertion into a tertiary C-H bond was successful, we envisioned that when cyclohexamethyl triflate was applied as the alkylating reagent, the subsequent reaction would provide a [5,6]-spiro ring system. Several natural products with a spiro-fused ring system are shown here (Scheme 2.22). Elisapterosin B exhibited strong inhibitory activity (79%) against M. tuberculosis H37Rv at a concentration of 12.5 μg/mL.[15] Conidiogenones B showed significant antibacterial activity against several methicillin-resistant bacteria species each with MIC value of 8 mg/ml.[16] Biological and clinic studies have shown that ingenol is a potent activator towards PKC and exhibited antitumor activity. Furthermore, some of the ingenol derivatives have been used as FDA approved drugs for treating skin cancer.[17]

Following the previously described route, alkylation with triflate **2.117** provided cyclohexane containing phosphonate **2.118** in 63% yield (Scheme 2.23). Diazo formation of **2.118** went smoothly to realize the desired diazo phosphonate **2.119**. Intramolecular C-H insertion reaction proved to be highly efficient, as the desired cyclized product **2.120** was formed in 95% yield. Thus we demonstrated that synthesis of the [5,6]-spiro ring system is possible.

We have also utilized this methodology for the construction of [5,7]-spiro ring system, as shown in Scheme 2.24. Starting from cycloheptamethyl triflate, similar protocols produced the cyclized product **2.124** in 91% yield.

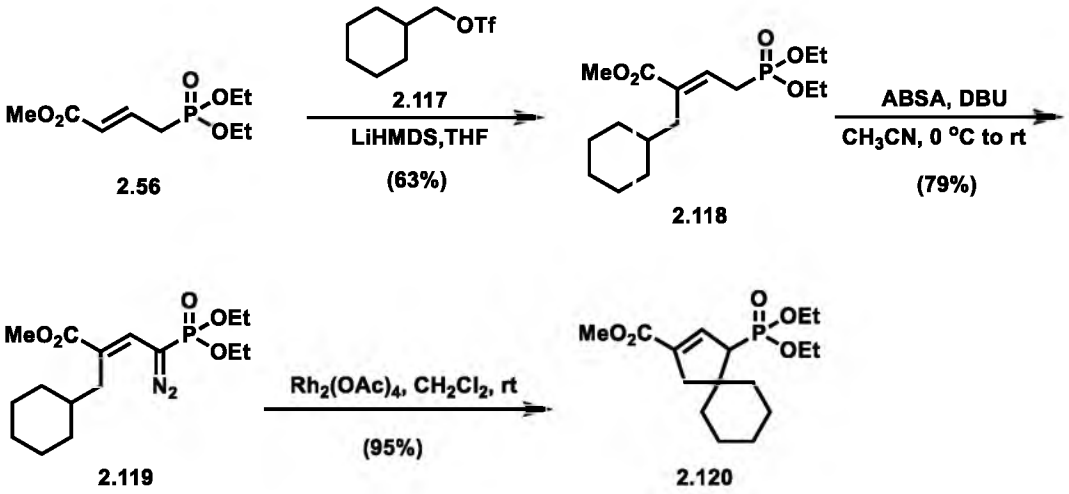


2.114
conidiogenone

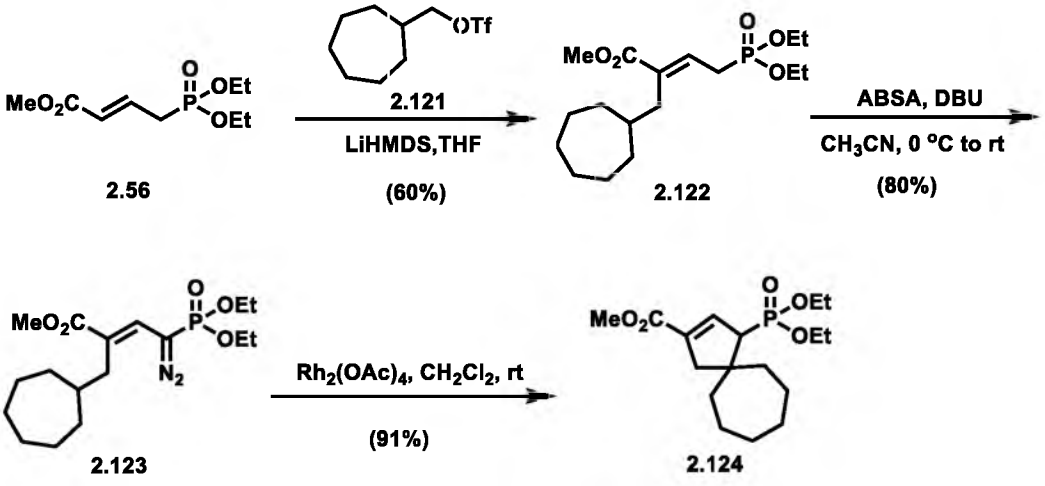
2.115
elisapterosin B

2.116
Ingenol

Scheme 2.22 Natural products containing spiro ring systems



Scheme 2.23 Synthesis of [5,6]-spiro ring system

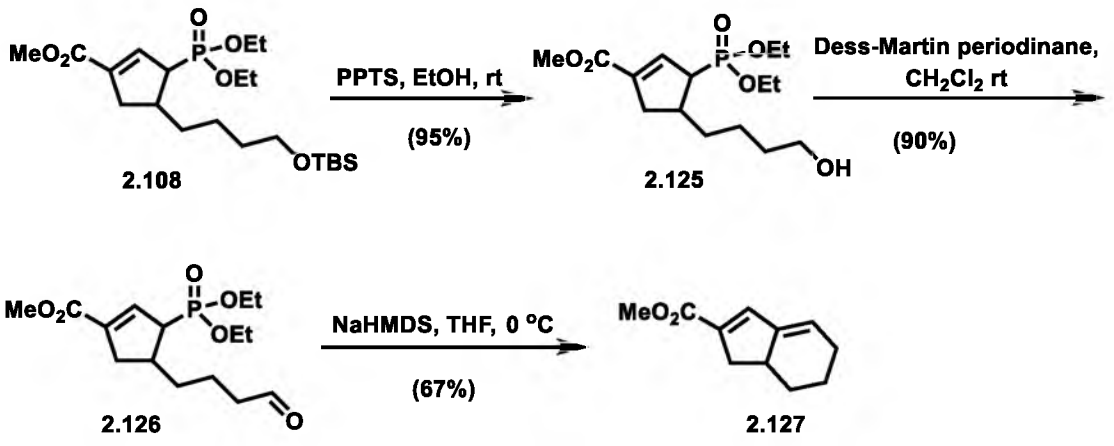


Scheme 2.24 Synthesis of [5,7]-spiro ring system

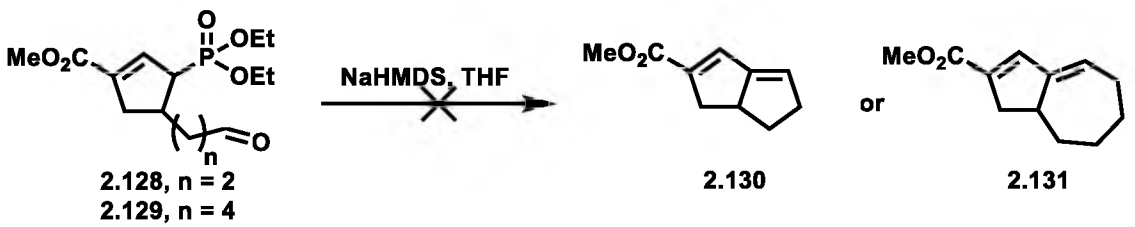
2.2.4 Synthesis of fused bicyclic carbocycles

Taking advantage of the labile phosphonate group, one can imagine that cyclopentenyl phosphonates are prone to Horner-Emmons reactions. Encouraged by the intermolecular Horner-Emmons reaction of **2.61** which provided the desired diene in moderate yield and diastereoselectivity, we set out to test whether the intramolecular Horner-Emmons reaction would give us a fused ring system such as [5,5], [5,6] and [5,7]- fused ring systems. The synthesis of [5,6]-fused system was examined first (Scheme 2.25). The suitable aldehyde substrate **2.126** was synthesized with no event from cyclopentene **2.108** by deprotecting the TBS group and oxidizing the resulting alcohol with Dess-Martin periodinane. The [5,6]-fused ring system **2.127** was successfully generated in 67% yield by treating the aldehyde with NaHMDS.

However, similar conditions to cyclize aldehyde **2.128** or **2.129** failed to provide corresponding [5,5] and [5,7]-fused ring systems (Scheme 2.26). Various conditions have been tested and only decomposition was observed.



Scheme 2.25 Synthesis of [5,6]-fused ring system



2.128, n = 2
2.129, n = 4

2.130

2.131

Scheme 2.26 Unsuccessful attempts towards [5,5] and [5,7]-fused systems

2.3 Conclusion

A series of vinyl diazo phosphonates were readily prepared from known phosphonocrotonate **2.56**. Methyl substituted vinyl diazo phosphonate **2.49** underwent a [3,3]-sigmatropic rearrangement to provide C-3 quaternary indoline **2.53**. In contrast, intramolecular C-H insertions took place to form cyclopentene phosphonates when treating diazo phosphonates **2.95** - **2.101** and **2.59** with $Rh_2(OAc)_4$. Both spiro and fused ring systems can be accessed using this methodology.

Future endeavors will include utilizing the intramolecular C-H insertion of diazo phosphonates in the synthesis of biological active small molecules. Carbocyclic nucleosides represent a type of promising targets for this methodology.

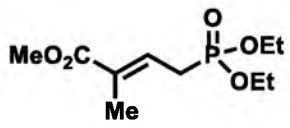
2.4 Experimental

NMR spectra were recorded on a Varian Inova-500, a Varian Unity-300, a Varian Inova-400 or a Varian VXR-500 spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to chloroform (7.25), benzene (7.16), or dichloromethane (5.29) as internal standards. Coupling constants, *J*,

were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Armarego. W. L. F. and Chai, C. L. L., Oxford, 2009). Spectroscopic grade CH_3CN was stored over activated 4Å molecular sieves and used without additional purification. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of dried nitrogen in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

2.4.1 General procedure for the alkylation of phosphonocrotonate

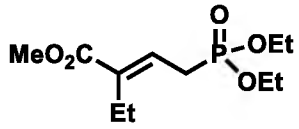
To a solution of phosphonocrotonate **2.56** (ca. 2.0 mmol) in 10 mL of THF at 0 °C was added LiHMDS (ca. 2.0 mmol) dropwise. After stirring at 0 °C for 0.5 h, the solution was warmed to rt and a solution of alkyl iodide or triflate (ca. 1.0 mmol) in 2 mL of THF was added dropwise. The resulting reaction mixture was stirred for 2 h and the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Flash chromatography provided the corresponding alkylated phosphonates.



2.47

(*E*)-methyl 4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.47). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.472 g, 2.00 mmol), THF (10 mL), LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) and MeI (62.3 µL, 1.00 mmol) in THF (2 mL) to give 0.188 g of **2.47** (75%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate).

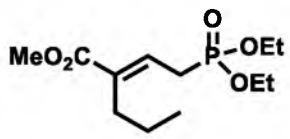
2.47: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 - 6.72 (m, 1H), 4.14 - 4.07 (m, 4H), 3.74 (s, 3H), 2.73 (ddd, *J* = 22.6, 8.3, 0.8 Hz, 2H), 1.90 - 1.87 (m, 3H), 1.38 - 1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (d, *J* = 3.5 Hz), 131.7 (d, *J* = 13.5 Hz), 130.7 (d, *J* = 11.0 Hz), 62.4 (d, *J* = 6.5 Hz), 52.2, 27.8 (d, *J* = 138.2 Hz), 16.7 (d, *J* = 6.0 Hz), 12.8 (d, *J* = 2.6 Hz); IR (neat) 2984, 1716, 1651, 1437, 1252, 1165, 1049, 1024, 965 cm^{-1}; LRMS m/z calcd for $C_{10}H_{19}O_5PNa$ 273.1 $[M+Na]^+$, found 273.0



2.58

(*E*)-methyl 4-(diethoxyphosphoryl)-2-ethylbut-2-enoate (2.58). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.472 g, 2.00 mmol), THF (10 mL), LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) and EtI (80.7 µL, 1.00 mmol) in THF (2 mL) to give 0.087 g of **2.58** (33%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate).

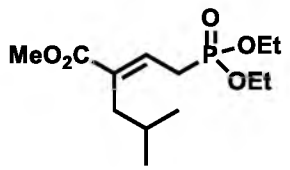
2.58: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (dt, *J* = 7.6, 7.6 Hz, 1H), 4.16 - 4.05 (m, 4H), 3.73 (s, 3H), 2.73 (dd, *J* = 23.4, 8.2 Hz, 2H), 2.33 (dq, *J* = 7.6, 2.2 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 137.7 (d, *J* = 14.1 Hz), 130.2 (d, *J* = 10.6 Hz), 62.4 (d, *J* = 6.5 Hz), 52.1, 27.5 (d, *J* = 139.5 Hz), 20.4 (d, *J* = 2.0 Hz), 16.7 (d, *J* = 6.1 Hz), 13.7 (d, *J* = 3.5 Hz); IR (neat) 2978, 1714, 1646, 1437, 1392, 1294, 1245, 1192, 1165, 1117, 1094, 1050, 1022, 963 cm^{-1}; LRMS m/z calcd for $C_{11}H_{21}O_5PNa$ 287.1 [M+Na]$^{+}$, found 287.1



2.87

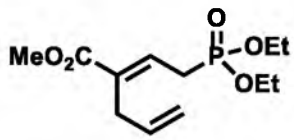
(*E*)-methyl 2-(2-(diethoxyphosphoryl)ethylidene)pentanoate (2.87). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.472 g, 2.00 mmol), THF (10 mL), LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) and PrI (97.5 µL, 1.00 mmol) in THF (2 mL) to give 0.0974 g of **2.87** (35%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate).

2.87: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (q, *J* = 7.8 Hz, 1H), 4.11 - 3.98 (m, 4H), 3.67 (s, 3H), 2.67 (dd, *J* = 23.1, 8.1 Hz, 2H), 2.27 - 2.19 (m, 2H), 1.37 (qt, *J* = 7.5, 1.8 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (d, *J* = 3.0 Hz), 136.2 (d, *J* = 14.0 Hz), 130.7 (d, *J* = 11.0 Hz), 62.4 (d, *J* = 7.0 Hz), 52.0, 28.9 (d, *J* = 2.0 Hz), 27.6 (d, *J* = 138.7 Hz), 22.4 (d, *J* = 3.5 Hz), 16.6 (d, *J* = 6.0 Hz), 14.2; IR (neat) 2961, 1712, 1284, 1251, 1222, 1164, 1018, 957, 853 820 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{23}O_5PNa$ 301.1[M+Na]$^{+}$, found 301.1



2.88

(*E*)-methyl 2-(2-(diethoxyphosphoryl)ethylidene)-4-methylpentanoate (2.88). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.472 g, 2.00 mmol), THF (10 mL), LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) and *i*-BuI (0.115 mL, 1.00 mmol) in THF (2 mL) to give 58.3 mg of **2.88** (20%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate). **2.88**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (q, *J* = 7.8 Hz, 1H), 4.11 - 3.89 (m, 4H), 3.67 (s, 3H), 2.68 (dd, *J* = 23.1, 8.1 Hz, 2H), 2.16 (dd, *J* = 7.2, 2.1 Hz, 2H), 1.70 (sep, *J* = 6.7 Hz, 1H), 1.25 (t, *J* = 6.9 Hz, 6H), 0.81 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 135.6 (d, *J* = 14.5 Hz), 131.3 (d, *J* = 10.1 Hz), 62.4 (d, *J* = 6.5 Hz), 52.1, 35.7 (d, *J* = 2.0 Hz), 28.4 (d, *J* = 2.6 Hz), 27.9 (d, *J* = 138.8 Hz), 22.6, 16.6 (d, *J* = 6.0 Hz); IR (neat) 2956, 1714, 1289, 1252, 1227, 1163, 1096, 1052, 1021, 961 cm^{-1}; LRMS m/z calcd for $C_{13}H_{25}O_5PNa$ 315.1 $[M+Na]^+$, found 315.1

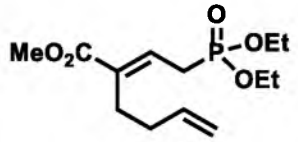


2.89

(*E*)-methyl 2-(2-(diethoxyphosphoryl)ethylidene)pent-4-enoate (2.89). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.709 g, 2.99 mmol), THF (15 mL), LiHMDS (3.15 mL of a 1.0 M solution in THF, 3.15 mmol) and allyl iodide (0.140 mL, 1.50 mmol) in THF (5 mL) to give 213 mg

of **2.89** (51%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate).

2.89: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dt, *J* = 8.1, 8.1 Hz, 1H), 5.79 (ddt, *J* = 17.0, 10.2, 6.0 Hz, 1H), 5.04 (ddt, *J* = 9.1, 1.8, 1.8 Hz, 1H), 4.99 (dd, *J* = 1.8, 1.8 Hz, 1H), 4.16 - 4.06 (m, 4H), 3.74 (s, 3H), 3.13 - 3.10 (m, 2H), 2.74 (dd, *J* = 23.2, 8.2 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 134.7 (d, *J* = 3.5 Hz), 133.6 (d, *J* = 14.1 Hz), 132.3 (d, *J* = 11.1 Hz), 115.9, 62.4 (d, *J* = 6.6 Hz), 52.2, 30.9 (d, *J* = 2.0 Hz), 27.6 (d, J = 139.5 Hz), 16.7 (d, *J* = 6.0 Hz); IR (neat) 2982, 1715, 1639, 1438, 1252, 1214, 1023, 963 cm^{-1}; LRMS m/z calcd for $C_{12}H_{21}O_5PNa$ 299.1 $[M+Na]^+$, found 299.1

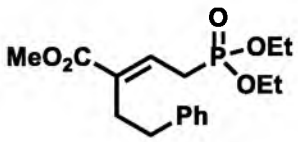


2.90

(*E*)-methyl 2-(2-(diethoxyphosphoryl)ethylidene)hex-5-enoate (2.90). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.472 g, 2.00 mmol), THF (10 mL), LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) and homoallyl triflate (0.124 mg, 0.600 mmol) in THF (2 mL) to give 75.8 mg of **2.90** (44%) as a colorless oil after flash chromatography (1:2 hexane/ethyl acetate).

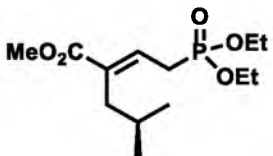
2.90: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (q, *J* = 8.1 Hz, 1H), 5.76 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.03 - 4.88 (m, 2H), 4.15 - 4.00 (m, 4H), 3.70 (s, 3H), 2.70 (dd, *J* = 23.3, 8.2 Hz, 2H), 2.38 (td, *J* = 7.9, 1.6 Hz, 2H), 2.12 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 137.8, 135.5 (d, *J* = 13.6 Hz), 131.3 (d, *J* = 10.6 Hz), 115.4, 62.4 (d, *J* = 7.0 Hz), 52.1, 33.1 (d, *J* = 3.0

Hz), 27.7 (d, *J* = 139.5 Hz), 26.5 (d, *J* = 2.0 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2981, 1713, 1642, 1249, 1163, 1020, 962 cm^{-1}; LRMS m/z calcd for $C_{13}H_{23}O_5PNa$ 313.1$[M+Na]^+$, found 313.1



2.91

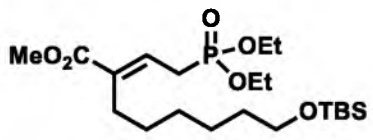
(*E*)-methyl 4-(diethoxyphosphoryl)-2-phenethylbut-2-enoate (2.91). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.472 g, 2.00 mmol), THF (10 mL), LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) and $PhCH_2CH_2OTf$ (0.300 g, 1.20 mmol) in THF (2 mL) to give 0.191 g of **2.91** (50%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate). **2.91**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 - 7.25 (m, 2H), 7.19 - 7.16 (m, 3H), 6.76 (q, *J* = 8.1 Hz, 1H), 4.12 - 4.03 (m, 4H), 3.75 (s, 3H), 2.74 - 2.69 (m, 2H), 2.64 - 2.58 (m, 2H), 2.48 (dd, *J* = 23.1, 8.0 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 141.6, 135.1 (d, *J* = 13.8 Hz), 131.8 (d, *J* = 10.6 Hz), 128.8 (d, *J* = 6.8 Hz), 128.7 (d, *J* = 9.8 Hz), 126.3, 62.4 (d, *J* = 8.3 Hz), 52.1, 35.2 (d, *J* = 3.0 Hz), 29.3 (d, *J* = 2.4 Hz), 27.3 (d, *J* = 138.1 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2981, 1712, 1437, 1248, 1195, 1174, 1095, 1019, 958 cm^{-1}; LRMS m/z calcd for $C_{17}H_{25}O_5PNa$ 363.1 $[M+Na]^+$, found 363.1.



2.92

(*S,E*)-methyl 5-(tert-butyldimethylsilyloxy)-2-(2-(diethoxyphosphoryl)ethylidene)-4- methylpentanoate (2.92). Prepared according to the general procedure using phosphonocrotonate **2.56** (59.3 mg, 2.00 mmol), THF (10 mL), LiHMDS (0.25 mL of a 1.0 M solution in THF, 0.25 mmol) and (R)-3-(*tert*-butyldimethylsilyloxy)-2-methylpropyl triflate (42.2 mg, 0.125 mmol) in THF (2 mL) to give 27.1 mg of **2.92** (51%) as a colorless oil after flash chromatography (1:2 hexane/ethyl acetate).

2.92: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (q, *J* = 8.1 Hz, 1H), 4.14 - 4.03 (m, 4H), 3.71 (s, 3H), 3.40 (d, *J* = 5.4 Hz, 2H), 2.83 (ddd, *J* = 15.1, 15.1, 8.3 Hz, 1 H), 2.71 (ddd, *J* = 15.3m 15.3, 8.1 Hz, 1 H), 2.48 (ddd, *J* = 13.8, 6.4, 2.3 Hz, 1H), 2.14 (ddd, *J* = 13.6, 8.0, 2.0 Hz, 1H), 1.84 - 1.67 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 6H), 0.875 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 135.2 (d, *J* = 14.0 Hz), 131.8 (d, *J* = 10.0 Hz), 67.5, 62.4 (d, *J* = 3.0 Hz), 62.3 (d, *J* = 2.6 Hz) , 52.1, 35.9 (d, *J* = 3.0 Hz), 30.1 (d, *J* = 2.6 Hz), 27.7 (d, *J* = 138.6 Hz), 26.1, 18.5, 16.8, 16.6 (d, *J* = 6.5 Hz), -5.2, -5.2; IR (neat) 2954, 2930, 2857, 1717, 1253, 1218, 1165, 1086, 1026, 964 cm^{-1}; LRMS m/z calcd for $C_{19}H_{39}O_6PSiNa$ 445.2 $[M+Na]^+$, found 445.1



2.93

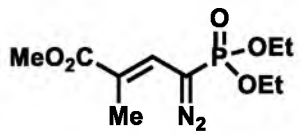
(*E*)-methyl 8-(tert-butyldimethylsilyloxy)-2-(2-(diethoxyphosphoryl) ethylidene) octanoate (2.93). Prepared according to the general procedure using phosphonocrotonate **2.56** (0.218 g, 0.920 mmol), THF (5 mL), LiHMDS (0.93 mL of a 1.0 M solution in THF, 0.93 mmol) and 5-(*tert*-

butyldimethylsilyloxy)pentyl trifluoromethanesulfonate (0.162g, 0.460 mmol) in THF (2 mL) to give 87.0 mg of **2.93** (51%) as a colorless oil after flash chromatography (1:1 hexanes:ethyl acetate).

2.93: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (q, *J* = 7.8 Hz, 1H), 4.16 - 4.05 (m, 4H), 3.73 (s, 3H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.72 (dd, *J* = 23.2, 8.2 Hz, 2H), 2.34 - 2.27 (m, 2H), 1.54 - 1.44 (m, 2H), 1.44 - 1.28 (m, 12H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8 (d, *J* = 3.2 Hz), 136.5 (d, *J* = 14.4 Hz), 130.6 (d, *J* = 10.7 Hz), 63.4, 62.4 (d, *J* = 7.0 Hz), 52.0, 33.0, 29.7, 29.3 (d, *J* = 3.2 Hz), 27.6 (d, *J* = 143.1 Hz), 27.1 (d, *J* = 1.1 Hz), 26.2, 25.9, 16.6 (d, *J* = 5.9 Hz), -5.1; IR (neat) 2930, 2857, 2360, 2341, 1717, 1652, 1254, 1097, 1054, 1026, 963, 836, 775 cm^{-1}; LRMS *m/z* calcd for $C_{21}H_{43}O_6PSiNa$ 473.2 $[M+Na]^+$, found 473.2

2.4.2 General procedure for diazo formation

To a solution of phosphonate (ca. 0.10 mmol) and ABSA in 5 mL CH_3CN at 0 °C was added DBU dropwise. The resulting reaction mixture was warmed to rt and stirred for 12 h. Following concentration, the resulting residue was taken up in CH_2Cl_2 (9 mL). Concentration and flash chromatography gave diazo compounds.

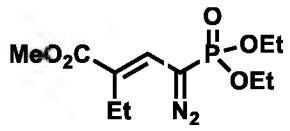


2.49

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.49). Prepared according to the general procedure using phosphonate **2.47** (0.200 g,

0.800 mmol), ABSA (0.211 g, 0. 880 mmol) and DBU (0.143 mL, 0. 960 mmol) to give 0.141 g of **2.49** (64%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

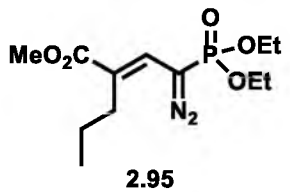
2.49: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (dq, *J* = 7.9, 1.2 Hz, 1H), 4.25 - 4.06 (m, 4H), 3.73 (s, 3H), 1.96 (d, *J* = 1.1 Hz, 3H), 1.35 (dt, *J* = 7.2, 0.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 124.7 (d, *J* = 10.6 Hz), 122.4 (d, *J* = 9.9 Hz), 63.4 (d, *J* = 5.3 Hz), 52.2, 16.3 (d, *J* = 6.9 Hz), 12.5; IR (neat) 2985, 2078, 1705, 1616, 1436, 1259, 1133, 1045, 1015, 973 cm^{-1}; LRMS m/z calcd for $C_{10}H_{17}N_2O_5PNa$ 299.1 $[M+Na]^+$, found 299.1.



2.59

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.59). Prepared according to the general procedure using phosphonate **2.58** (0.106 g, 0.401 mmol), ABSA (0.106 g, 0.44 mmol) and DBU (72.2 µL, 0.48 mmol) to give 85 mg of **2.59** (73%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

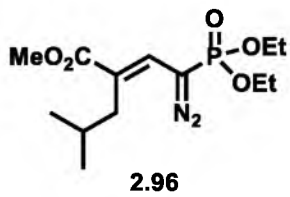
2.59: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (d, *J* = 8.1 Hz, 1H), 4.25 - 4.06 (m, 4H), 3.73 (s, 3H), 2.37 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 128.5 (d, *J* = 9.9 Hz), 124.1 (d, *J* = 11.4 Hz), 63.5 (d, *J* = 5.3 Hz), 52.1, 20.0, 16.4 (d, *J* = 6.9 Hz), 14.9; IR (neat) 2981, 2078, 1706, 1610, 1436, 1277, 1237, 1134, 1045, 1016, 973 cm^{-1}; LRMS m/z calcd for $C_{11}H_{19}N_2O_5PNa$ 313.1$[M+Na]^+$, found 313.0.



2.95

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.95). Prepared according to the general procedure using phosphonate **2.87** (52.7 mg, 0.190 mmol), ABSA (50.0 mg, 0.210 mmol) and DBU (34.0 µL, 0.227 mmol) to give 44.6 mg of **2.95** (77%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

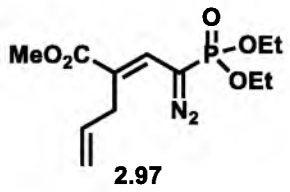
2.95: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, *J* = 8.3 Hz, 1H), 4.25 - 4.06 (m, 4H), 3.72 (s, 3H), 2.34 - 2.29 (m, 2H), 1.49 - 1.35 (partially obscured m, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 127.2 (d, *J* = 10.6 Hz), 124.4 (d, *J* = 10.6 Hz), 63.5 (d, *J* = 5.3 Hz), 52.1, 28.5, 23.6, 16.4 (d, *J* = 6.1 Hz), 13.8; IR (neat) 2961, 2074, 1706, 1607, 1436, 1268, 1218, 1190, 1137, 1046, 1017, 973 cm^{-1}; LRMS m/z calcd for $C_{12}H_{21}N_2O_5PNa$ 327.1 $[M+Na]^+$, found 327.1.



2.96

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.96). Prepared according to the general procedure using phosphonate **2.88** (29.1 mg, 0.100 mmol), ABSA (26.4 mg, 0.11 mmol) and DBU (18.0 µL, 0.12 mmol) to give 23.6 mg of **2.96** (74%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

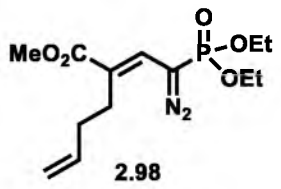
2.96: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, *J* = 8.3 Hz, 1H), 4.25 - 4.06 (m, 4H), 3.73 (s, 3H), 2.24 (d, *J* = 7.4 Hz, 2H), 1.71 (sep, *J* = 6.9 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 126.5 (d, *J* = 10.6 Hz), 124.7 (d, *J* = 11.4 Hz), 63.5 (d, *J* = 5.3 Hz), 52.1, 34.6, 29.1, 22.1, 16.4 (d, *J* = 6.9 Hz); IR (neat) 2958, 2870, 2076, 1707, 1605, 1270, 1221, 1139, 1046, 1017, 973 cm^{-1}; LRMS m/z calcd for $C_{13}H_{23}N_2O_5PNa$ 341.1[M+Na]$^{+}$, found 341.1.



2.97

(*E*)-methyl 2-(2-diazo-2-(diethoxyphosphoryl)ethylidene)pent-4-enoate (2.97). Prepared according to the general procedure using phosphonate **2.89** (200 mg, 0.724 mmol), ABSA (191 mg, 0.796 mmol) and DBU (0.13 mL, 0.87 mmol) to give 148 mg of **2.97** (67%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

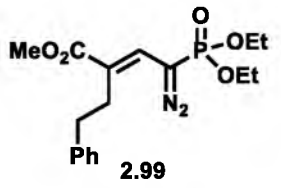
2.97: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 1H), 5.92 - 5.79 (m, 1H) 5.09 - 4.96 (m, 2H), 4.25 - 4.08 (m, 4H), 3.74 (s, 3H), 3.16 - 3.13 (m, 2H), 1.36 (t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5,135.6, 126.5 (d, *J* = 11.1 Hz), 123.2 (d, *J* = 10.3 Hz), 115.7, 63.5 (d, *J* = 5.3 Hz), 52.3, 30.1, 16.4 (d, J = 6.9 Hz); IR (neat) 2983, 2078, 1706, 1608, 1437, 1267, 1204, 1016, 973 cm^{-1}; LRMS m/z calcd for $C_{12}H_{19}N_2O_5PNa$ 325.1[M+Na]$^{+}$, found 325.1.



2.98

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.98). Prepared according to the general procedure using phosphonate **2.90** (38.0 mg, 0.120 mmol), ABSA (34.6 mg, 0.144 mmol) and DBU (23.5 µL, 0.160 mmol) to give 31.4 mg of **2.98** (76%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

2.98: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, *J* = 8.2 Hz, 1H), 5.78 (ddt, *J* = 16.9, 10.0, 6.7 Hz, 1H), 5.04 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H), 4.99 (ddt, *J* = 10.1, 1.8, 1.1 Hz, 1H), 4.26-4.06 (m, 4H), 3.74 (s, 3H), 2.47 - 2.42 (m, 2H), 2.21 - 2.11 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 137.1, 126.1 (d, *J* = 10.6 Hz), 124.9 (d, *J* = 11.4 Hz), 115.9, 63.5 (d, *J* = 5.3 Hz), 52.2, 34.1, 26.1, 16.4 (d, *J* = 6.1 Hz); IR (neat) 2982, 2076, 1705, 1608, 1436, 1260, 1198, 1137, 973 cm^{-1}; LRMS m/z calcd for $C_{13}H_{21}N_2O_5PNa$ 339.1 $[M+Na]^+$, found 339.1.

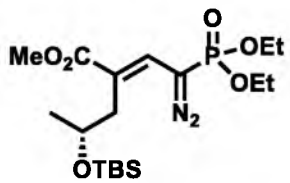


2.99

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.99). Prepared according to the general procedure using phosphonate **2.91** (38.0 mg, 0.112 mmol), ABSA (29.6 mg, 0.120 mmol) and DBU (20.1 µL, 0.135 mmol) to

give 35.2 mg of **2.99** (86%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

2.99: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 - 7.26 (m, 2H), 7.22 - 7.17 (m, 3H), 6.64 (d, *J* = 8.4 Hz, 1H), 4.22 - 4.02 (m, 4H), 3.76 (s, 3H), 2.76 - 2.60 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 141.1, 128.7, 128.7, 126.5, 125.9 (d, *J* = 10.0 Hz), 125.2 (d, *J* = 11.0 Hz), 63.5 (d, *J* = 5.5 Hz), 52.2, 36.2, 29.0, 16.4 (d, *J* = 6.5 Hz); IR (neat) 2984, 2951, 2077, 1705, 1609, 1261, 1191, 1165, 1045, 1016, 974 cm^{-1}; LRMS m/z calcd for $C_{17}H_{23}N_2O_5PNa$ 389.1 $[M+Na]^+$, found 389.1.

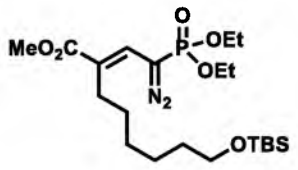


2.100

(*E*)-methyl 4-diazo-4-(diethoxyphosphoryl)-2-methylbut-2-enoate (2.100). Prepared according to the general procedure using phosphonate **2.92** (14.5 mg, 0.0343 mmol), ABSA (9.1 mg, 0.0379 mmol) and DBU (6.2 μL, 0.041 mmol) to give 12.8 mg of **2.100** (83%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

2.100: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, *J* = 8.4 Hz, 1H), 4.26 - 4.06 (m, 4H), 3.73 (s, 3H), 3.45 (d, *J* = 5.9 Hz, 2H), 2.48 (dd, *J* = 14.3, 6.0 Hz, 1H), 2.19 (dd, *J* = 14.2, 9.0 Hz, 1H), 1.87 - 1.70 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 125.8 (d, *J* = 10.5 Hz), 124.9 (d, *J* = 11.0 Hz), 68.2, 63.5 (d, *J* = 5.6 Hz), 52.1, 36.5, 29.7, 26.2, 18.6, 16.4 (d, *J* = 7.0 Hz), 16.1, -5.2, -5.2; IR (neat)

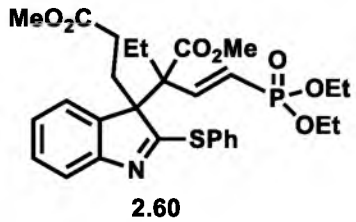
2954, 2930, 2857, 2075, 1708, 1607, 1472, 1435, 1260, 1210, 1090, 1048, 1019, 973 cm^{-1}; LRMS m/z calcd for $C_{19}H_{37}N_2O_6PSiNa$ 471.2 $[M+Na]^+$, found 471.1.



2.101

(*E*)-methyl-8-(tert-butyldimethylsilyloxy)-2-(2-diazo-2(diethoxyphosphoryl) ethylidene) octanoate 2.101. Prepared according to the general procedure using phosphonate **2.93** (0.142 g, 0.320 mmol), ABSA (83 mg, 0.35 mmol) and DBU (56.0 µL, 0.375 mmol) to give 0.115 g of **2.101** (77%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate)

2.101: ^1H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, *J* = 8.3 Hz, 1H), 4.20 - 4.10 (m, 4H), 3.72 (s, 3H), 3.58 (t, *J* = 6.6 Hz, 2H),), 2.33 (t, *J* = 7.8 Hz, 2H), 1.53 - 1.46 (m, 2H), 1.42 - 1.30 (m, 12H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 127.4 (d, *J* = 10.2 Hz), 124.2 (d, *J* = 10.7 Hz), 63.5 (d, *J* = 5.3 Hz), 63.4, 52.1, 33.0, 30.5, 29.5, 26.7, 26.2, 25.8, 16.4 (d, *J* = 7.0 Hz), -5.1; IR (neat) 2930, 2857, 2360, 2341, 2075, 1707, 1608, 1435, 1258, 1095, 1018, 973, 836, 775 cm^{-1}; LRMS *m/z* calcd for $C_{21}H_{41}N_2O_6PSi$ 499.2 $[M+Na]^+$, found 499.2



2.60

(*E*)-methyl 4-(diethoxyphosphoryl)- 2-ethyl- 2-(3-(3-methoxy-3-oxopropyl)-2-(phenylthio) -3H-indol-3-yl)but-3-enoate (2.60). To a solution of thioindole **2.50** (14.3 mg, 45.9 µmol) and $Rh_2(OAc)_4$ (1.0 mg, 2.3 µmol) in CH_2Cl_2 (2 mL) at

rt was added a solution of diazophosphonate **2.49** (40.0 mg, 0.138 mmol) in CH_2Cl_2 (2 mL) over 4 h via syringe pump. After stirring at rt for 24 h, the reaction mixture was concentrated. Flash chromatography (1:2 hexane/ ethyl acetate) gave 7.1 mg of indoline **2.60** (27%) as a pale yellow oil.

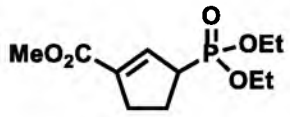
2.60: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 - 7.62 (m, 2H), 7.46 - 7.41 (m, 3H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.07 (dt, *J* = 7.3, 1.0 Hz, 1H), 6.97 (dd, *J* = 23.9, 18.1 Hz, 1H), 5.61 (dd, *J* = 18.3, 18.3 Hz, 1H), 4.02 - 3.88 (m, 4H), 3.75 (s, 3H), 3.54 (s, 3H), 2.74 - 2.57 (m, 2H), 2.24 - 2.16 (m, 1H), 2.00 - 1.86 (m, 2H), 1.34 - 1.24 (m, 7H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 173.3, 171.5, 155.4, 147.2 (d, *J* = 6.9 Hz), 138.3, 134.8, 129.7, 129.6, 129.1, 128.2, 124.5, 123.7, 121.0 (d, *J* = 184.6 Hz), 120.0, 68.7 (d, *J* = 1.5 Hz), 62.1 (d, *J*= 5.3 Hz), 62.0 (d, *J*= 5.3 Hz), 58.5 (d, *J* = 19.9 Hz), 52.2, 51.8, 29.0, 27.4, 24.2, 16.6, 16.5, 9.9 IR (neat) 2981, 1734, 1514, 1456, 1441, 1250, 1213, 1170, 1052, 1023, 965, 849, 748 cm^{-1}; LRMS m/z calcd for $C_{28}H_{35}NO_7PS$ 574.2 $[M+H]^+$, found 574.2

2.4.3 General procedure for cyclopentene formation

To a solution of vinyl diazophosphonate (ca. 0.10 mmol) in CH_2Cl_2 was added $Rh_2(OAc)_4$ (ca. 0.005 mmol) in one portion. After stirring at rt overnight, the reaction mixture was concentrated. The resulting residue was purified by flash chromatography to give cyclopentenes.

2.4.4 General procedure for equilibration

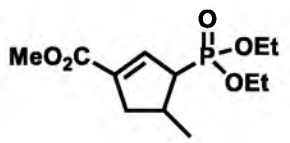
To a solution of the cyclopentene **2.103**, **2.105** or **2.106** in CH_2Cl_2 was added 0.05 mL of DBU dropwise. The reaction mixture was allowed to stir for 1 h before it was concentrated. Preparative TLC (1:2 hexane/ethyl acetate) gave cyclopentenes as single isomers as determined by 1H NMR analysis in 70% ~ 80% yield.



2.61

Methyl 3-(diethoxyphosphoryl)cyclopent-1-enecarboxylate (2.61). Prepared according to the general procedure using diazo **2.59** (147 mg, 0.510 mmol) and $Rh_2(OAc)_4$ (11 mg, 0.025 mmol) to give 91.1 mg of cyclopentene **2.61** (68%) as a colorless oil after flash chromatography (1:2 to 1:3 hexane/ethyl acetate).

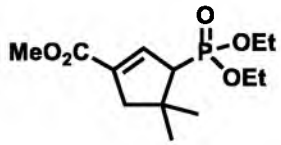
2.61: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dddd, *J* = 4.7, 2.2, 2.2, 2.2 Hz, 1H), 4.17 - 4.05 (m, 4H), 3.73 (s, 3H), 3.28-3.13 (m, 1H), 2.80 - 2.54 (m, 2H), 2.37 - 2.15 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (d, *J* = 3.0 Hz), 139.5 (d, *J* = 14.0 Hz), 138.4 (d, *J* = 9.0 Hz), 62.5 (d, *J* = 7.0 Hz), 62.3 (d, *J* = 7.1 Hz), 51.9, 44.5 (d, *J* = 143.2 Hz), 31.5 (d, *J* = 3.5 Hz), 24.7 (d, *J* = 3.0 Hz), 16.7 (d, *J* = 5.5 Hz); IR (neat) 2982, 1717, 1438, 1257, 1214, 1163, 1094, 1053, 1023 cm^{-1}; LRMS m/z calcd for $C_{11}H_{19}O_5PNa$ 285.1 $[M+Na]^+$, found 285.0



2.103

Methyl 3-(diethoxyphosphoryl)-4-methylcyclopent-1-enecarboxylate (2.103). Prepared according to the general procedure using diazo **2.95** (22.3 mg, 0.0730 mmol) and $Rh_2(OAc)_4$ (1.6 mg, 0.0037 mmol) to give 18.1 mg of cyclopentene **2.103** (89%) as a colorless oil after flashchromatography (1:2 to 1:3 hexane/ethyl acetate).

2.103 (after equilibration using DBU): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (dddd, *J* = 4.6, 2.2, 2.2, 2.2 Hz, 1H), 4.18 - 4.05 (m, 4H), 3.74 (s, 3H), 2.99 - 2.86 (m, 1H), 2.84 - 2.65 (m, 2H), 2.32 - 2.18 (m, 1H), 1.31 (dt, *J* = 7.2, 0.3 Hz 3 H), 1.30 (dt, *J* = 7.4, 0.3 Hz, 3H), 1.14 (dd, *J* = 6.8, 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 138.1 (d, *J* = 13.5 Hz), 137.5 (d, *J* = 9.0 Hz), 62.4 (d, *J* = 7.1 Hz), 62.3 (d, *J* = 6.9 Hz), 52.5 (d, *J* = 141.6 Hz), 51.9, 39.9 (d, *J* = 4.0 Hz), 33.8 (d, *J* = 2.0 Hz), 22.2 (d, *J* = 9.5 Hz), 16.7 (d, *J* = 5.6 Hz); IR (neat) 2959, 1718, 1635, 1438, 1249, 1092, 1052, 1024, 959 cm^{-1}; LRMS m/z calcd for $C_{12}H_{21}O_5PNa$ 299.1 $[M+Na]^+$, found 299.0

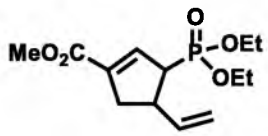


2.104

Methyl 3-(diethoxyphosphoryl)-4,4-dimethylcyclopent-1-enecarboxylate (2.104). Prepared according to the general procedure using diazo **2.96** (11.8 mg, 0.037 mmol) and $Rh_2(OAc)_4$ (0.8 mg, 0.0018 mmol) to give 9.3 mg of cyclopentene **2.104** (86%) as a colorless oil after flash chromatography (1:2 to 1:3 hexane/ethyl acetate).

2.104: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 - 6.59 (m, 1H), 4.18 - 4.02 (m, 4H), 3.73 (s, 3H), 2.82 (dddd, *J* = 25.8, 2.6, 2.6, 1.6 Hz, 1H), 2.58 (dddd, *J* = 16.1, 6.9, 2.3,

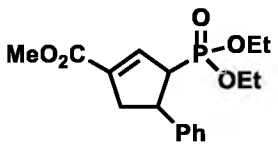
2.3 Hz, 1H), 2.37 (dddd, *J* = 16.2, 7.4, 1.6, 1.6 Hz, 1H), 1.34 - 1.27 (m, 9H), 1.18 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (d, *J* = 3.0 Hz), 138.7 (d, *J* = 9.5 Hz), 137.9 (d, *J* = 13.1 Hz), 62.1 (d, *J* = 7.0 Hz), 62.0 (d, *J* = 7.5 Hz), 55.1 (d, *J* = 138.7 Hz), 51.8, 46.7 (d, *J* = 2.6 Hz), 42.3, 31.3 (d, *J* = 10.5 Hz), 25.6 (d, *J* = 5.5 Hz), 16.7 (d, *J* = 6.0 Hz); IR (neat) 2980, 1718, 1437, 1247, 1164, 1053, 1025 cm^{-1}; LRMS m/z calcd for $C_{13}H_{23}O_5PNa$ 313.1 $[M+Na]^+$, found 313.0.



2.105

Methyl 3-(diethoxyphosphoryl)-4-vinylcyclopent-1-enecarboxylate (2.105). Prepared according to the general procedure using diazo **2.98** (15.7 mg, 0.0496 mmol) and $Rh_2(OAc)_4$ (1.1 mg, 0.0025 mmol) to give 11.9 mg of cyclopentene **2.105** (83%) as a colorless oil after flash chromatography (1:2 to 1:3 hexane/ethyl acetate).

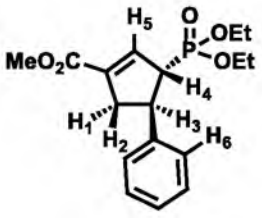
2.105 (after DBU equilibration): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 - 6.60 (m, 1H), 5.85 (ddd, *J* = 17.6, 10.3, 7.8 Hz, 1H), 5.12-5.08 (m, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 4.15 - 4.07 (m, 4H), 3.74 (s, 3H), 3.35 - 3.25 (m, 1H), 3.04 (ddd, *J* = 7.9, 5.4, 3.2 Hz, 1H), 3.00-2.93 (m, 1 H), 2.55 - 2.48 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (d, *J* = 3.1 Hz), 140.5 (d, *J* = 8.4 Hz), 138.0 (d, *J* = 13.7 Hz), 137.4 (d, *J* = 9.2 Hz), 114.7 (d, *J* = 2.3 Hz), 62.6 (d, *J* = 7.0 Hz), 62.4 (d, *J* = 6.9 Hz), 51.9, 50.7 (d, *J* = 142.7 Hz), 42.7 (d, *J* = 2.3 Hz), 37.9 (d, *J* = 3.8 Hz), 16.7 (d, *J* = 1.5 Hz), 16.7 (d, *J* = 2.3 Hz); IR (neat) 2982, 1719, 1635, 1438, 1249, 1096, 1053, 1024, 962 cm^{-1}; LRMS m/z calcd for $C_{13}H_{21}N_2O_5PNa$ 311.1 $[M+Na]^+$, found 311.1.



2.106

Methyl 3-(diethoxyphosphoryl)-4-phenylcyclopent-1-enecarboxylate (2.106). Prepared according to the general procedure using diazo **2.99** (17.6 mg, 0.0480 mmol) and $Rh_2(OAc)_4$ (1.1 mg, 0.0024 mmol) to give 11.9 mg of cyclopentene **2.106** (78%) as a colorless oil after flash chromatography (1:2 to 1:3 hexane/ethyl acetate).

2.106 (after DBU equilibration): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.16 (m, 5H), 6.72 (dddd, *J* = 6.2, 2.3, 2.3, 2.3 Hz, 1H), 4.13 - 3.98 (m, 4H), 3.90 - 3.77 (m, 1H), 3.77 (s, 3H), 3.35 - 3.16 (m, 2H), 2.86 - 2.72 (m, 1H), 1.25 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9 (d, *J* = 3.0 Hz), 145.5 (d, *J* = 8.4 Hz), 138.2 (d, *J* = 13.7 Hz), 137.4 (d, *J* = 8.4 Hz), 129.0, 127.1, 126.9, 62.6 (d, *J* = 6.9 Hz), 62.4 (d, *J* = 6.9 Hz), 53.6 (d, *J* = 141.9 Hz), 51.9, 44.1 (d, *J* = 1.5 Hz), 40.8 (d, *J* = 4.6 Hz), 16.7 (d, *J* = 6.1 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2983, 2951, 1718, 1634, 1495, 1438, 1391, 1349, 1250, 1195, 1162, 1097, 1023 cm^{-1}; LRMS m/z calcd for $C_{17}H_{23}O_5PNa$ 361.1 $[M+Na]^+$, found 361.0.



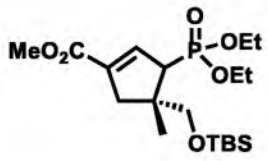
Summary of 1D NOE data for the single isomer of compound **2.106** after equilibration (500 Hz, C_6D_6):

Irradiation at 2.80 ppm (H-1) resulted in enhancement at 3.30 ppm (H-3) and 7.05 ppm (H-5);

Irradiation at 3.30 ppm (H-3) resulted in enhancement at 2.80 ppm (H-1);

Irradiation at 3.20 ppm (H-2) resulted in enhancement at 7.05 ppm (H-5), 6.85 ppm (H-6), 3.80 ppm (H-4) and 2.80 ppm (H-1);

Irradiation at 3.90 ppm (H-4) resulted in enhancement at 7.05 ppm (H-5) and 3.20 ppm (H-2).



2.107

(4*S*)-methyl 4-((tert-butyldimethylsilyloxy)methyl)-3-(diethoxyphosphoryl)-4-methyl cyclopent-1-enecarboxylate (2.107). Prepared according to the general procedure using diazo **2.100** (93.1 mg, 0.208 mmol) and $Rh_2(OAc)_4$ (4.6 mg, 0.010 mmol) to give 79.0 mg of cyclopentene **1.180** (91%, 3:2 mixture of isomers) as a colorless oil after flash chromatography (1:2 to 1:3 hexanes/ethyl acetate). Analytically pure **2.107** (major isomer) was obtained following preparatory TLC (1:2 hexanes/ethyl acetate). The minor isomer could not be separated from the major isomer.

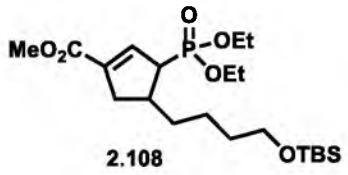
2.107 (major isomer): $[\alpha]_D^{25}$ = -48.0 (c = 0.125, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 - 6.60 (m, 1H), 4.15 - 4.04 (m, 4H), 3.82 (d, *J* = 9.8 Hz, 1H), 3.74 (s, 3H), 3.70 (d, *J* = 8.8 Hz, 1H), 2.89 - 2.78 (m, 2H), 2.32 (dddd, *J* = 17.1, 7.8, 2.0, 2.0 Hz,1H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.21 (broad s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 138.0 (d, *J* = 9.1 Hz), 137.9, 67.8 (d, *J* =

6.0 Hz), 62.3 (d, *J* = 7.1 Hz), 62.0 (d, *J* = 7.6 Hz), 53.6 (d, *J* = 137.6 Hz), 51.8, 47.8, 42.2 (d, *J* = 3.0 Hz), 26.1, 25.8 (d, *J* = 9.6 Hz), 18.5, 16.7 (d, *J* = 6.0 Hz), -5.2 (d, *J* =1.5 Hz); IR (neat) 2954, 2929, 2856, 1721, 1472, 1438, 1249, 1198, 1086, 1053, 1027 cm^{-1}; LRMS m/z calcd for $C_{19}H_{37}O_6PSiNa$ 443.2 $[M+Na]^+$, found 443.1.

Complete chirality retention in C-H insertion reactions is identified by HPLC separation of compound 28 (chiral OD-H column, 0.5 ml/min, 98:2 hexane/isopropanol)

28 from racemic diazo 18: t_R = 7.92 min (50%), 24.68 (50%)

28 from chiral diazo 18: t_R = 7.80 min



Methyl 4-(4-(tert-butyldimethylsilyloxy)butyl)-3-(diethoxyphosphoryl) cyclopent-1-enecarboxylate 2.108. Prepared according to the general procedure using diazo **2.101** (0.115 g, 0.242 mmol) and $Rh_2(OAc)_4$ (5.4 mg, 0.012 mmol) to give 0.102 g of cyclopentene **2.108** (94%) as a colorless oil after flash chromatography (1:2 hexane/ethyl acetate).

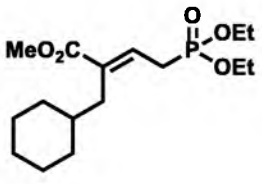
2.108: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 - 6.57 (m, 1H), 4.14 - 4.05 (m, 4H), 3.73 (s, 3H), 3.58 (t, *J* = 6.6 Hz, 2H),), 2.92 - 2.80 (m, 2H), 2.70 - 2.57 (m, 1H), 2.35 - 2.27 (m, 1H), 1.56 - 1.47 (m, 3H), 1.40 - 1.27 (m, 9H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 138.2 (d, *J* = 13.3 Hz), 137.5 (d, *J* = 9.6 Hz), 63.2, 62.4 (d, *J* = 7.3 Hz), 62.3 (d, *J* = 6.9 Hz), 51.8, 50.8 (d, *J* = 142.4 Hz), 38.8 (d, *J* = 2.3 Hz), 37.9 (d, *J* = 3.2 Hz), 36.5 (d, *J* = 8.7 Hz), 32.9, 26.2, 23.6, 16.7 (d,

J = 5.5 Hz), -5.0; IR (neat) 2931, 2857, 2361, 2340, 1718, 1436, 1252, 1096, 1025, 959, 836, 775 cm^{-1}; LRMS *m/z* calcd for $C_{21}H_{41}O_6PSi$ 449.2 $[M+H]^+$, found 449.2

2.109

Methyl 1-(diethoxyphosphoryl)bicyclo[3.1.0]hex-2-ene-3-carboxylate (2.109). To a solution of vinyl diazophosphonate **2.97** (20.0 mg, 61.7 µmol) in CH_2Cl_2 (2 mL) was added $Cu(CH_3CN)_4PF_6$ (1.2 mg, 3.2 µmol) in one portion. After stirring for 5 min the reaction mixture was concentrated and flash chromatography (1:2 hexane/ethyl acetate) provided 14.9 mg of desired product **2.109** (82%) as a colorless oil.

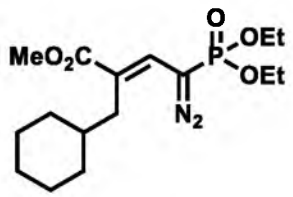
2.109: ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (dt, *J* = 1.9 Hz, 1H), 4.17 - 4.00 (m, 4H), 3.70 (s, 3H), 2.89 (ddt, *J* = 18.0, 5.2, 1.8 Hz, 1H), 2.70 (dd, *J* = 18.1, 9.1 Hz, 1H), 2.33 - 2.22 (m, 1H), 1.67 (ddd, *J* = 13.2, 8.2, 4.0 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.59 (q, *J* = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 143.7 (d, *J* = 6.5 Hz), 135.3 (d, *J* = 122.1 Hz), 62.4 (d, *J* = 6.1 Hz), 51.8, 34.6, 29.8 (d, *J* = 205.0 Hz), 23.9 (d, *J* = 3.0 Hz), 22.8, 16.7 (d, *J* = 6.1 Hz), 16.6 (d, *J* = 6.0 Hz); IR (neat) 2984, 2920, 1718, 1617, 1438, 1249, 1025, 964, 942 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{19}O_5PNa$ 297.1 $[M+H]^+$, found 297.1.



2.118

(*E*)-methyl 2-(cyclohexylmethyl)-4-(diethoxyphosphoryl)but-2-enoate 2.118. Prepared according to the general procedure using phosphonocrotonate **2.56** (0.236 g, 1.00 mmol), THF (5 mL), LiHMDS (1.0 mL of a 1.0 M solution in THF, 1.0 mmol) and cyclohexylmethyl trifluoromethanesulfonate (0.169g, 0.686 mmol) in THF (2 mL) to give 0.142 g of **2.118** (59%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate).

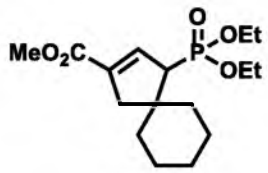
2.118: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (q, *J* = 7.9 Hz, 1H), 4.17 - 4.05 (m, 4H), 3.72 (s, 3H), 2.72 (dd, *J* = 23.3, 8.1 Hz, 2H), 2.21 (dd, *J* = 7.1, 1.7 Hz, 2H), 1.70 - 1.57 (m, 5H), 1.44 - 1.34 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 6H), 1.20 - 1.07 (m, 3H), 0.93 - 0.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 (d, *J* = 2.3 Hz), 135.2 (d, *J* = 14.5 Hz), 131.3 (d, *J* = 10.7 Hz), 62.4 (d, *J* = 6.7 Hz), 52.1, 37.9 (d, *J* = 2.3 Hz), 34.5, 33.4, 27.9 (d, *J* = 139.6 Hz), 26.6, 26.5, 16.6 (d, *J* = 6.1 Hz); IR (neat) 2982, 2923, 2851, 2360, 2340, 1716, 1645, 1448, 1249, 1024, 963, 820 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{29}O_5P$ 355.2 $[M+Na]^+$, found 355.2



2.119

(*E*)-methyl 2-(cyclohexylmethyl)-4-diazo-4-(diethoxyphosphoryl)but-2-enoate 2.119. Prepared according to the general procedure using phosphonate **2.118** (41 mg, 0.12 mmol), ABSA (32 mg, 0.13 mmol) and DBU (22 µL, 0.15 mmol) to give 36 mg of **2.119** (82%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

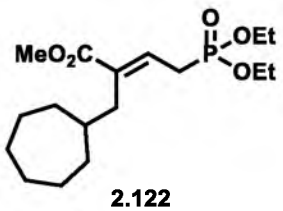
2.119: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, *J* = 8.3 Hz, 1H), 4.22 - 4.08 (m, 4H), 3.72 (s, 3H), 2.23 (d, *J* = 7.3 Hz, 2H), 1.72 - 1.60 (m, 6H), 1.36 (t, *J* = 7.1 Hz, 6H), 1.22 - 1.10 (m, 3H), 0.96 - 0.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 126.2 (d, *J* = 10.7 Hz), 124.6 (d, *J* = 11.2 Hz), 63.5 (d, *J* = 5.4 Hz), 52.1, 38.8 (d, *J* = 2.7 Hz), 33.4, 32.9, 26.6 (d, *J* = 3.6 Hz), 16.4 (d, *J* = 6.9 Hz); IR (neat) 2984, 2924, 2851, 2360, 2341, 2071, 1705, 1604, 1435, 1262, 1016, 972, 753 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{27}N_2O_5P$ 381.2 $[M+Na]^+$, found 381.2



2.120

Methyl 4-(diethoxyphosphoryl)spiro[4.5]dec-2-ene-2-carboxylate **2.120**. Prepared according to the general procedure using diazo **2.119** (29.9 mg, 0.083 mmol) and $Rh_2(OAc)_4$ (1.8 mg, 4.2 μmol) to give 24.0 mg of cyclopentene **2.120** (89%) as a colorless oil after flash chromatography (1:2 hexane/ethyl acetate).

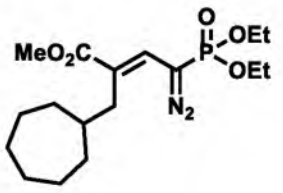
2.120: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 - 6.60 (m, 1H), 4.14 - 4.03 (m, 4H), 3.73 (s, 3H), 2.80 (dd, *J* = 15.9, 2.8 Hz, 1H), 2.56 (d, *J* = 7.8 Hz, 2H), 1.92 - 1.86 (m, 1H), 1.78 (dt, *J* = 12.5, 3.3 Hz, 1H), 1.67 (td, *J* = 13.0, 3.9 Hz, 1H), 1.62 - 1.50 (m 3H), 1.50 - 1.40 (m, 3H), 1.36 - 1.20 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5 (d, *J* = 3.8 Hz), 138.7 (d, *J* = 10.0 Hz), 137.6 (d, *J* = 13.0 Hz), 62.0 (d, *J* = 6.9 Hz), 61.9 (d, *J* = 7.6 Hz), 56.3 (d, *J* = 137.3 Hz), 51.8, 46.4, 41.2, 38.2 (d, *J* = 11.5 Hz), 34.3 (d, *J* = 6.1 Hz), 26.0, 23.6, 23.0, 16.7 (d, *J* = 3.8 Hz), 16.7 (d, *J* = 4.6 Hz); IR (neat) 2981, 2928, 2855, 1716, 1635, 1437, 1245, 1051, 1024, 957, 742 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{27}O_5P$ 353.2 $[M+H]^+$, found 353.1



2.122

(*E*)-methyl 2-(cycloheptylmethyl)-4-(diethoxyphosphoryl)but-2-enoate 2.122. Prepared according to the general procedure using phosphonocrotonate **2.56** (0.236 g, 1.00 mmol), THF (5 mL), LiHMDS (1.0 mL of a 1.0 M solution in THF, 1.0 mmol) and cycloheptylmethyl trifluoromethanesulfonate (0.159g, 0.610 mmol) in THF (2 mL) to give 0.116 g of **2.122** (55%) as a colorless oil after flash chromatography (1:2 hexanes:ethyl acetate).

2.122: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (q, *J* = 7.9 Hz, 1H), 4.16 - 4.05 (m, 4H), 3.74 (s, 3H), 2.74 (dd, *J* = 22.9, 8.1 Hz, 2H), 2.27 - 2.21 (m, 2H), 1.72 - 1.24 (m, 17H), 1.19 - 1.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 (d, *J* = 3.2 Hz), 135.7 (d, *J* = 14.4 Hz), 131.3 (d, *J* = 10.2 Hz), 62.4 (d, *J* = 6.4 Hz), 52.1, 39.5 (d, *J* = 2.7 Hz), 34.9 (d, *J* = 2.1 Hz), 34.6, 28.5, 27.9 (d, *J* = 139.4 Hz), 26.3, 16.6 (d, *J* = 6.4 Hz); IR (neat) 2982, 2921, 2853, 2359, 2341, 1715, 1645, 1437, 1254, 1023, 961, 818, 765 cm^{-1}; LRMS *m/z* calcd for $C_{17}H_{31}O_5P$ 355.2 $[M+Na]^+$, found 355.2

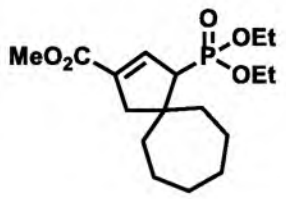


2.123

(*E*)-methyl 2-(cycloheptylmethyl)-4-diazo-4-(diethoxyphosphoryl)but-2-enoate 2.123. Prepared according to the general procedure using phosphonate **2.122** (54 mg, 0.16 mmol), ABSA (42 mg, 0.17 mmol) and DBU (28 µL, 0.19

mmol) to give 48 mg of **2.123** (83%) as a clear orange oil after flash chromatography (2:1 hexane/ethyl acetate).

2.123: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, *J* = 8.3 Hz, 1H), 4.22 - 4.08 (m, 4H), 3.72 (s, 3H), 2.26 (d, *J* = 7.3 Hz, 2H), 1.68 - 1.52 (m, 7H), 1.50 - 1.42 (m, 2H), 1.38 - 1.30 (m, 8H), 1.18 - 1.10 (m, 2H), 0.96 - 0.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 126.6 (d, *J* = 10.4 Hz), 124.7 (d, *J* = 11.2 Hz), 63.5 (d, *J* = 5.3 Hz), 52.1, 40.4, 34.3, 34.0, 28.4, 26.6, 16.4 (d, *J* = 6.9 Hz); IR (neat) 2984, 2922, 2853, 2360, 2341, 2070, 1704, 1603, 1436, 1261, 1015, 971, 760 cm^{-1}; LRMS *m/z* calcd for $C_{17}H_{29}N_2O_5P$ 395.2 $[M+Na]^+$, found 395.2

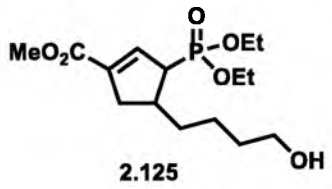


2.124

Methyl 4-(diethoxyphosphoryl)spiro[4.6]undec-2-ene-2-carboxylate 2.124. Prepared according to the general procedure using diazo **2.123** (43 mg, 0.11 mmol) and $Rh_2(OAc)_4$ (2.5 mg, 5.7 μmol) to give 34 mg of cyclopentene **2.124** (86%) as a colorless oil after flash chromatography (1:2 hexane/ethyl acetate).

2.124: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 - 6.60 (m, 1H), 4.14 - 4.02 (m, 4H), 3.72 (s, 3H), 2.84 (d, *J* = 25.9 Hz, 1H), 2.58 (dd, *J* = 16.1, 7.8 Hz, 2H), 2.47 (dd, *J* = 16.6, 7.6 Hz, 1H), 2.13 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.81 (dd, *J* = 14.4, 8.1 Hz, 1H), 1.71 (dd, *J* = 13.9, 8.1 Hz, 1H), 1.66 - 1.36 (m, 9H), 1.33 - 1.22 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 139.2 (d, *J* = 10.7 Hz), 137.7 (d, *J* = 13.0 Hz), 62.1 (d, *J* = 7.6 Hz), 62.0 (d, *J* = 6.9 Hz), 56.7 (d, *J* = 136.6 Hz), 51.8, 49.8, 44.3, 42.6(d, *J* = 12.2 Hz), 36.4 (d, *J* = 5.3 Hz), 29.9 (d, J = 7.6 Hz), 24.1, 23.0, 16.7 (d, *J* = 2.3

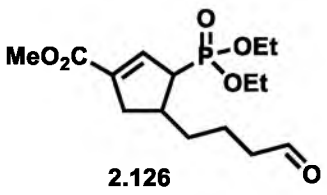
Hz), 16.7 (d, *J* = 2.3 Hz); IR (neat) 2980, 2921, 2853, 1715, 1635, 1437, 1241, 1051, 1022, 957, 740 cm^{-1}; LRMS *m/z* calcd for $C_{17}H_{29}O_5P$ 367.2 $[M+H]^+$, found 367.1



2.125

Methyl 3-(diethoxyphosphoryl)-4-(4-hydroxybutyl)cyclopent-1-enecarboxylate 2.125. To a solution of cyclopentene **2.108** (0.274 g, 0.611 mmol) in 190 proof ethanol (5 mL) at rt was added PPTS (0.153 g, 0.612 mmol) in one portion. The reaction mixture was allowed to react at rt for 6 h. Concentrate and flash chromatography (10:1 ethyl acetate/ethanol) provided 0.191 g of alcohol **2.125** (94%) as a colorless oil.

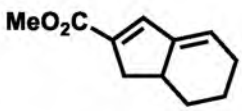
2.125: ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 - 6.55 (m, 1H), 4.15 - 4.04 (m, 5H), 3.72 (s, 3H), 3.62 (dt, *J* = 6.2, 1.1 Hz, 2H), 2.94 - 2.81 (m, 2H), 2.64 - 2.60 (m, 1H), 2.36 - 2.26 (m, 1H), 1.96 (br, 1H), 1.58 - 1.48 (m, 3H), 1.41 - 1.33 (partially obscure, m, 2H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 138.1 (d, *J* = 13.0 Hz), 137.4 (d, *J* = 9.2 Hz), 62.5 (d, *J* = 6.9 Hz), 62.4 (d, *J* = 6.1 Hz), 51.8, 50.7 (d, *J* = 142.7 Hz), 38.5, 37.9 (d, *J* = 3.1 Hz), 36.4 (d, *J* = 8.4 Hz), 32.6, 23.5, 16.7 (d, *J* = 5.3 Hz); IR (neat) 3413, 2931, 2859, 1717, 1635, 1438, 1237, 11051, 1021, 963 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_{27}O_6PNa$ 357.2 $[M+H]^+$, found 357.2.



2.126

Methyl 3-(diethoxyphosphoryl)-4-(4-oxobutyl)cyclopent-1-enecarboxylate 2.126. To a solution of alcohol **2.125** (25 mg, 0.073mmol) in CH_2Cl_2 (3 mL) at rt was added DMP (93 mg, 0.22 mmol) in one portion. The reaction mixture was allowed to react at rt for 4 h. The reaction was quenched with $NaHCO_3$ (aq., 5 mL) and separated. The aqueous phase was extracted with 5 mL EtOAc three times and the combined organic phase was dried and concentrated. Flash chromatography (1:20 hexane/ethyl acetate) provided 22 mg of aldehyde **2.126** (88%) as a colorless oil.

2.126: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.57 - 6.57 (m, 1H), 4.13 - 4.06 (m, 4H), 3.72 (s, 3H), 2.92 - 2.83 (m, 1H), 2.67 - 2.59 (m, 1H), 2.45 (t, *J* = 6.4 Hz, 2H), 2.35 - 2.29 (m, 1H), 1.69 - 1.52 (m, 3H), 1.43 - 1.35 (partially obscure, m, 2H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 165.1, 138.1 (d, *J* = 13.4 Hz), 137.4 (d, *J* = 9.2 Hz), 62.5 (d, *J* = 6.7 Hz), 62.4 (d, *J* = 7.3 Hz), 51.9, 50.7 (d, *J* = 143.4 Hz), 43.8, 38.6 (d, *J* = 2.5 Hz), 37.9 (d, *J* = 3.7 Hz), 36.0 (d, *J* = 10.2 Hz), 19.8, 16.7 (d, *J* = 6.1 Hz); IR (neat) 2929. 2854, 1719, 1633, 1440, 1247, 1052, 1023, 962 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_2O_6P$ 330.1[M+H]$^+$, found 330.1



2.127

Methyl 5,6,7,7α-tetrahydro-1H-indene-2-carboxylate (2.127). To a solution of aldehyde **2.126** (23.0 mg, 0.0699 mmol) in THF (3 mL) at 0 °C was added NaHMDS (0.10 mL, 1M solution in THF, 0.10 mmol) dropwise. The reaction mixture was allowed to react at 0 °C for 10 min. Concentrate and flash chromatography provided 8.1 mg of **2.127** (65%) as a colorless oil.

2.127: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 5.75 (dt, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 2.78 (dd, *J* = 15.2, 8.4 Hz, 1H), 2.73 - 2.62 (m, 1H), 2.28 - 2.13 (m, 3H), 2.10 - 2.02 (m, 1H), 1.89 - 1.84 (m, 1H). 1.64 - 1.68 (m, 1H), 1.35 - 1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 147.0, 141.7, 137.0, 123.3, 51.4, 40.1, 36.9, 28.1, 25.3, 22.5; IR (neat) 2926, 2854, 1714, 1653, 1587, 1436, 1244, 1086 cm^{-1}; LRMS *m/z* calcd for $C_{11}H_{14}O_2Na$ 201.1 $[M+Na]^+$, found 201.1.

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CHAPTER 3

DIAZO VINYL PHOSPHONATES AS PRECURSORS TOWARDS THE SYNTHESIS OF DYSIHERBAINE ANALOGS

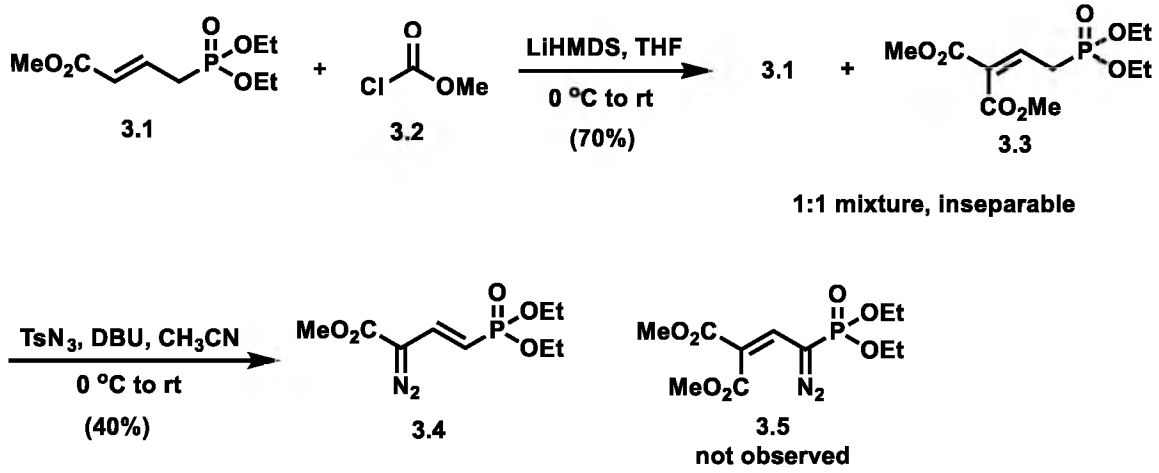
3.1 Synthesis of diazo vinyl phosphonate

In our effort to prepare malonate derived diazo phosphonate **3.5**, acylation of phosphonocrotonate **3.1** with methyl chloroformate **3.2** provided an inseparable mixture of the desired acylation product **3.3** and starting material **3.1** (Scheme 3.1). When subjecting this mixture to diazo transfer condition using tosyl azide as the diazo transfer reagent, surprisingly, diazo vinyl phosphonate **3.4** was obtained in good yield.

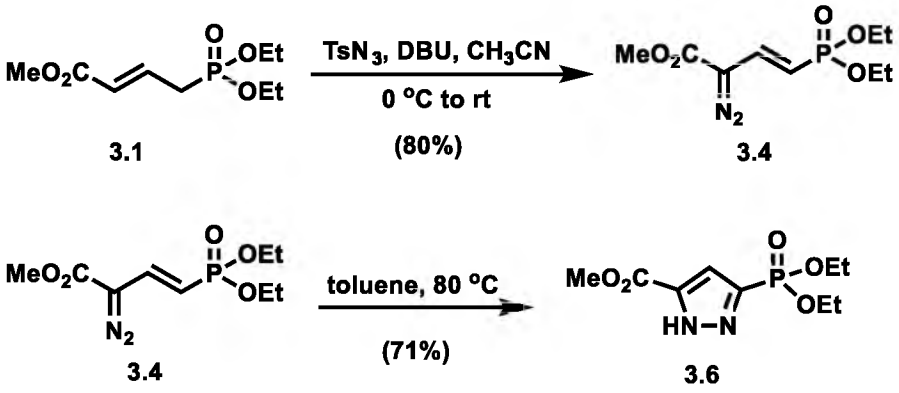
We were very excited about this result because it indicated that diazo compound directly derived from phosphonocrotonate **3.1** was actually accessible. The fact that the diazo functionality was formed solely adjacent to the ester group was confirmed by ^{13}C NMR. Higher yield was achieved by directly treating phosphonocrotonate **3.1** with TsN_3 and DBU (Scheme 3.2). The resulting diazo compound **3.4** was quite stable as it could be stored in benzene at -30 °C for a month. Upon heating, the diazo vinyl phosphonate **3.4** readily formed diazine **3.6** in good yield.

At this stage, we revisited the diazo transfer reaction of phosphonocrotonate **3.1** using ABSA as the diazo transfer reagent (Scheme 3.3). Crude NMR clearly showed that the desired diazo vinyl phosphonate **3.4** was formed; however, because diazo **3.4**, ABSA and the side product 4-acetamidobenzenesulfonamide had the same Rf value, further purification was not trivial. In the end, we were able to separate the desired product **3.4** from ABSA and sulfonamide taking advantage of their differences in solubility. After flash chromatography, washing the diazo compound/sulfonamide/ABSA coelute with a minimal amount of chloroform provided pure diazo **3.4** as indicated by ^{1}H NMR, although the yield was much lower than that using TsN_3 as diazo transfer reagent. The difficult purification and the limited stability of the diazo compound are probably the reason why we were not able to identify the desired diazo product previously.

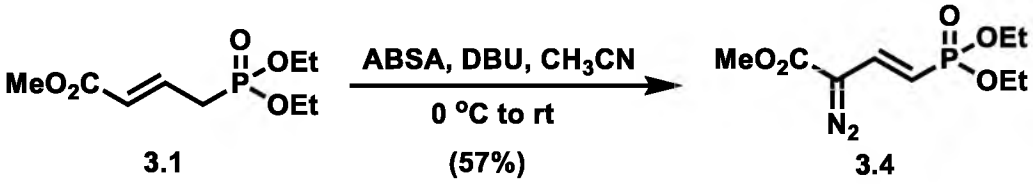
Phosphonate is generally recognized as an electron-withdrawing group, so this new diazo ester is considered to be an acceptor-acceptor type diazo compound. However, the electron-withdrawing effect of a phosphonate is much weaker than a corresponding ester, as indicated by the acidity of their α-proton: pK_a of the α-proton of malonate **3.7** is 15.7 while the pK_a of the α-proton of phosphonoester **3.8** is 18.6 (Scheme 3.4).[1] Interestingly, the pK_a of the α-proton of the benzyl ester **3.9** is only 23.6 and the corresponding metal carbenoid is considered to be a donor-acceptor carbenoid, it suggests that the reactivity of the metal carbenoid derived from diazo vinyl phosphonate **3.4** might fall between the traditional acceptor-acceptor metal carbenoids and the donor-acceptor carbenoids.



Scheme 3.1 Unexpected discovery of diazo vinyl phosphonate



Scheme 3.2 Synthesis of diazo vinyl phosphonate and its stability



Scheme 3.3 Synthesis of vinyl diazo phosphnate using ABSA

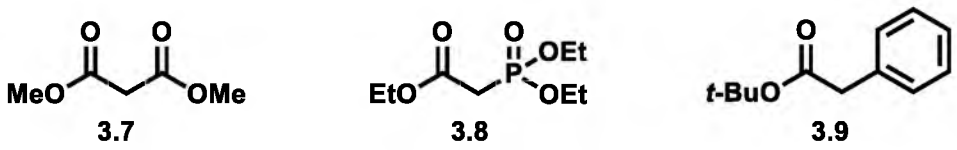
3.2 X-H Insertions of diazo vinyl phosphonates

3.2.1 Introduction

Given its long history, X-H insertion of metal carbenoids where X is oxygen, nitrogen or sulfur haven't received much attention from the synthetic community.[2] The reason might be that synthesis of α-functionalized carbonyl compounds can be accomplished by classic nucleophilic substitution reactions. However, compared to traditional methods, X-H insertions have several advantages. X-H insertions take place using mild and neutral conditions allowing a number of functional groups to be tolerated. The utilization of rhodium catalysts in X-H insertions provides very high turnovers. Compared to other transformations of metal carbenoids such as C-H insertions or cyclopropanations, X-H insertions are the preferred process.

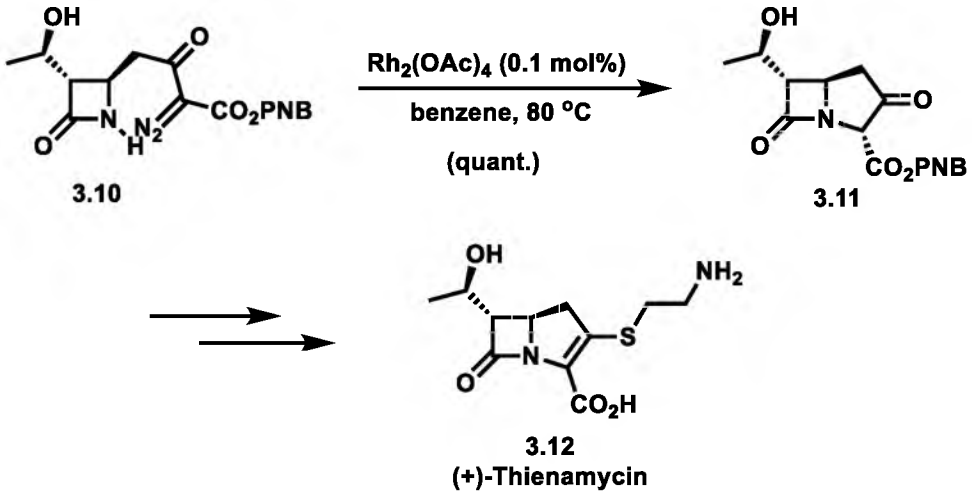
An early milestone that illustrated the synthetic utility of X-H insertion of metal carbenoids was Merck's total synthesis of thienamycin in 1980 (Scheme 3.5).[3] The pyrrolidine **3.11** was formed by an intramolecular N-H insertion in essentially quantitative yield. This example showcased the competency of the N-H insertion reaction in constructing highly strained and complex ring systems.

The Yang group reported the total synthesis of Maoecrystal V where an intramolecular O-H insertion was applied to assemble the key intermediate **3.14** (Scheme 3.6).[4] When treated with $Rh_2(OAc)_4$, diazo phosphonate **3.13** underwent a chemoselective O-H insertion reaction to give seven-membered product **3.14**, even in the presence of an alkene and an electron-rich aromatic system.

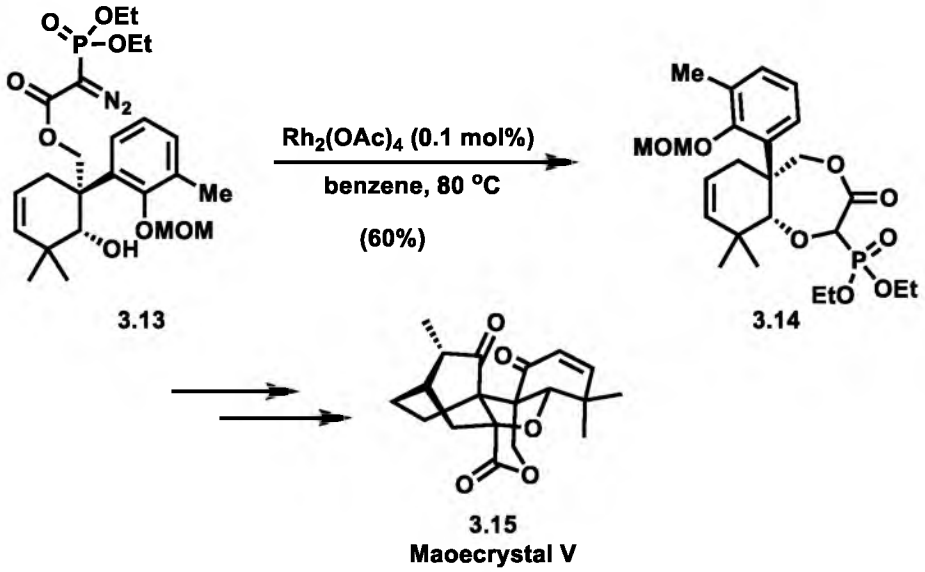


	3.7	3.8	3.9
pK_a in DMSO	15.3	18.6	23.6

Scheme 3.4 pKa value of related esters



Scheme 3.5 Merck's total synthesis of (+)-Thienamycin

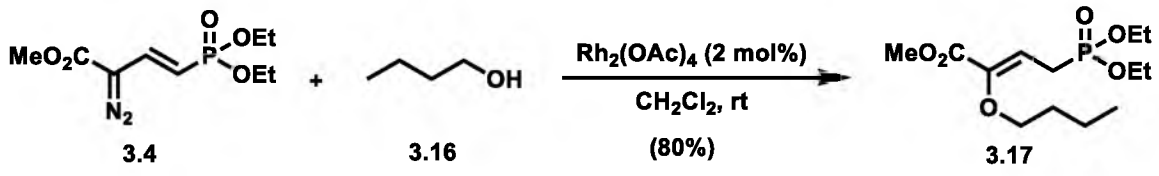


Scheme 3.6 Yang's total synthesis of Maoecrystal V

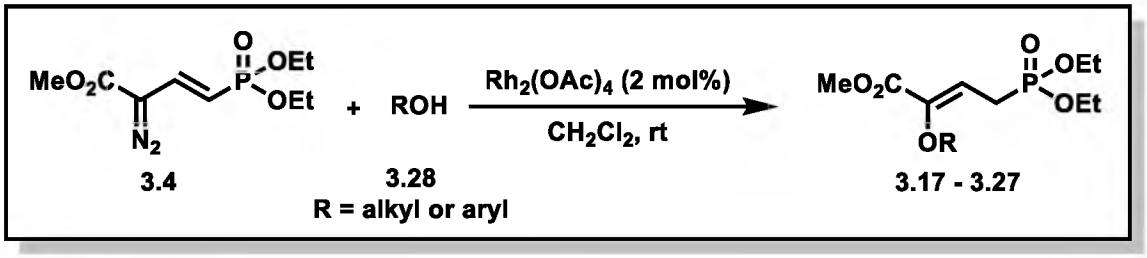
3.2.2 O-H Insertion of diazo vinyl phosphonates

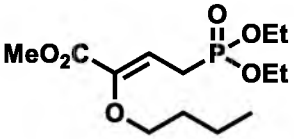
To explore the ability of diazo vinyl phosphonate **3.4** to undergo X-H insertions, we first tested its reaction with *n*-butyl alcohol (Scheme 3.7). To our delight this reaction proceeded very efficiently in the absence of a syringe pump for slow addition, giving the O-H insertion product in 80% yield. Furthermore, this reaction was highly stereoselective as only the *Z*-enol ether isomer was formed as determined by NOE experiment. This result suggested that *Z*-vinyl ethers could be prepared via an O-H insertion of metal carbenoids derived from diazo phosphonate **3.4**.

We next investigated the substrate scope of the O-H insertion reaction (Scheme 3.8). Secondary alcohols such as isopropanol underwent smooth O-H insertion and gave desired vinyl ether **3.18** in 84% yield. Allyl alcohol also participated in the O-H insertion to realize **3.19** and notably no cyclopropanation or C-H insertion product was formed. Similarly, highly chemoselective O-H insertions took place when homoallyl alcohol and alkynyl alcohols were evaluated. In addition, phenol reacted with vinyl diazo phosphonate and provided compound **3.25** in good yield. Iodo- and bromohydrins were also examined and the O-H insertion products **3.26** and **3.27** were isolated.

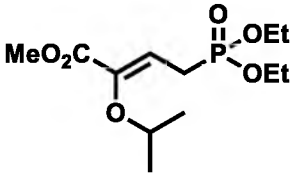


Scheme 3.7 O-H insertion of *n*-butyl alcohol

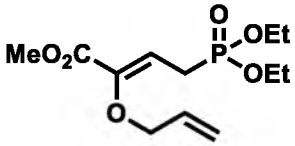




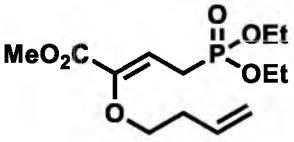
3.17, 82%



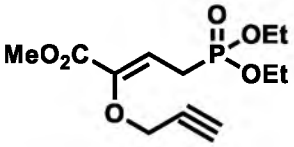
3.18, 84%



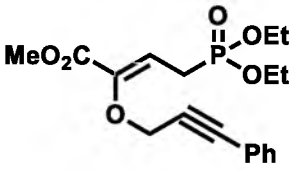
3.19, 85%



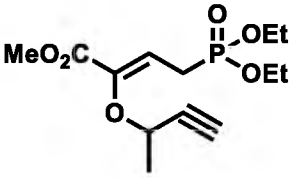
3.20, 82%



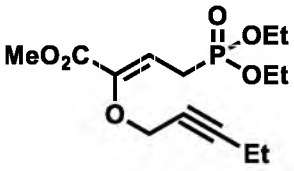
3.21, 73%



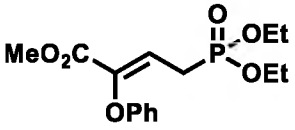
3.22, 84%



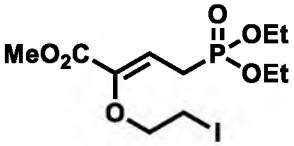
3.23, 68%



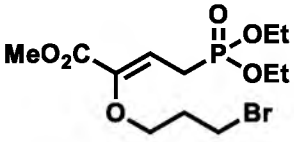
3.24, 73%



3.25, 70%



3.26, 79%



3.27, 74%

Scheme 3.8 O-H insertion: substrate scope

When a tertiary alcohol 1,1-dimethyl propargyl alcohol **3.29** was utilized, only a complex mixture was formed (Scheme 3.9). We suspect that competing ylide formation and subsequent transformations were involved.[5]

In all of the experiments described in Scheme 3.8, two equivalents of alcohols relative to the diazo compound were used. Catalyst loading was between 2 mol% and 0.2 mol%. In this way, we have developed a rapid and efficient route towards a diverse array of *Z*-vinyl ethers.

3.2.3 N-H Insertion of diazo vinyl phosphonates

Inspired by the successful O-H insertion reactions, we next explored other X-H insertion reactions. We first focused on N-H insertions (Scheme 3.10). When *tert*-butyl carbamate was treated with diazo vinyl phosphonate **3.4** in the presence of $Rh_2(OAc)_4$, desired N-H insertion product **3.31** was formed in good yield as a single isomer. NOE experiment confirmed the *Z*-geometry of the double bond which is consistent with the O-H insertion results. The metal carbenoid also inserted into the more electron-deficient N-H bond of toluenesulfonamide to realize enamine **3.32**. When acetamide was used, elevated reaction temperatures had to be applied, presumably in order to break the coordination of acetamide with the rhodium catalyst. We were also able to incorporate aniline into the phosphonate to give product **3.34**. A very interesting substrate turned out to be *N*-Boc guanidine. The N-H insertion with guanidine in the presence of $Rh_2(OAc)_4$ only resulted in recovery of the starting material. In our previous experiments $Rh_2(esp)_2$ catalyst was a more efficient catalyst and

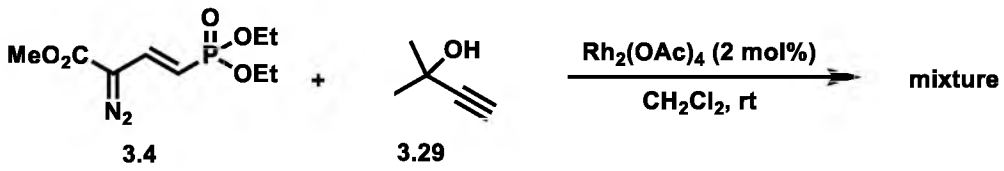
more robust against substrate binding. 4Å molecular sieves were also added to remove the methanol generated in the subsequent in situ cyclization. Using these optimized conditions we successfully obtained the cyclic guanidine product **3.35** in 56% yield. This product was characterized as the reduced product **3.36** which was formed by treating **3.35** with Pd/C under a H_2 atmosphere. It is worthwhile to mention that once converted to phosphonic acids, these N-H insertion products in physiological pH resemble glutamate, which is an important neurotransmitter.[6]

3.2.4 S-H Insertion of diazo vinyl phosphonates

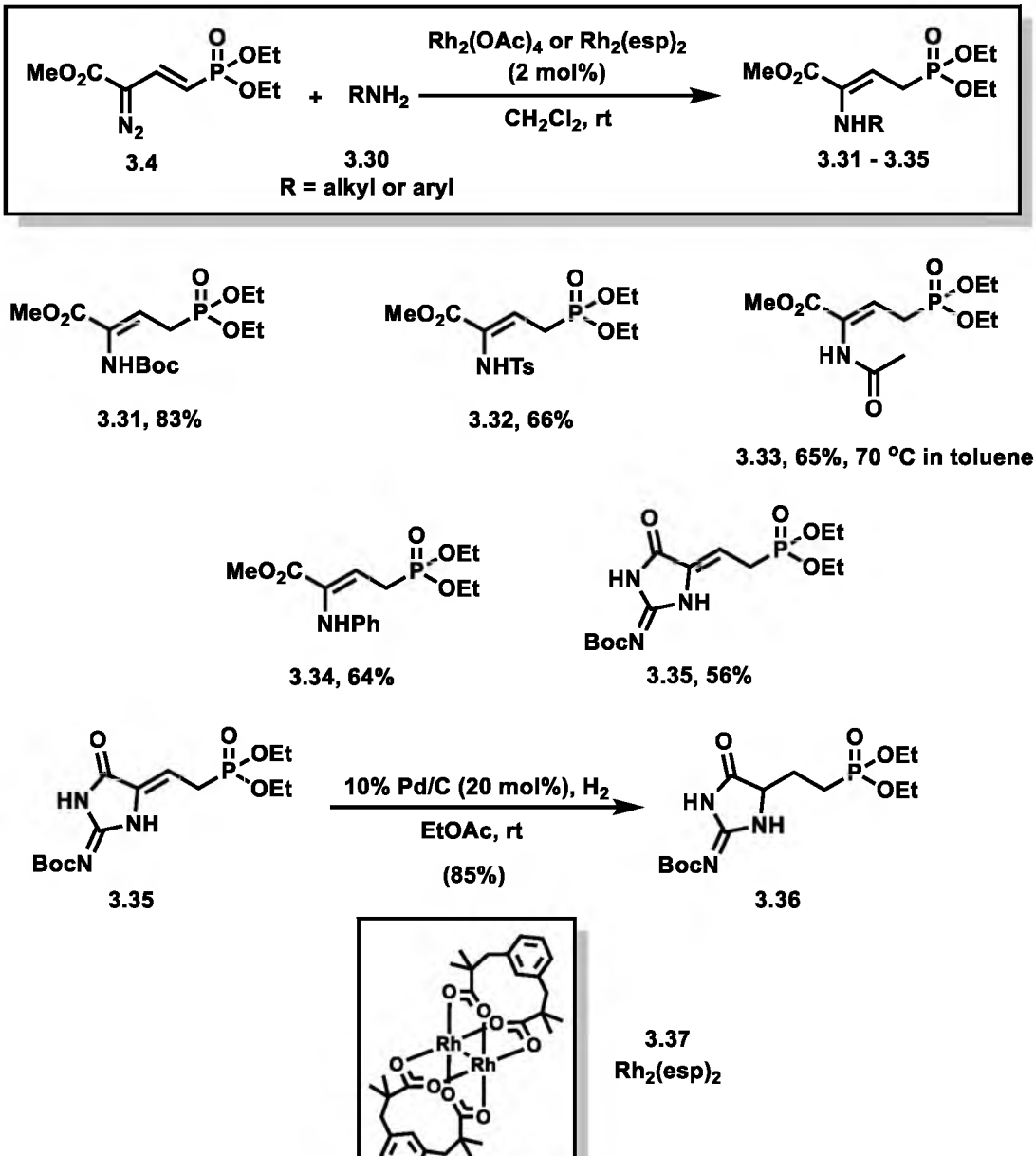
We also carried out the S-H insertion reaction of thiophenol to give product **3.38** in good yield (Scheme 3.11).

3.2.5 Competition study of X-H insertion reactions

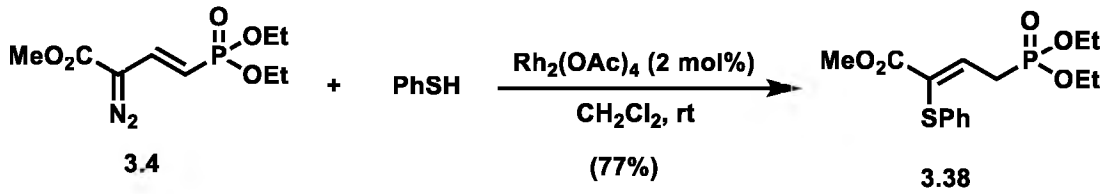
As mentioned earlier, compared to C-H insertion and cyclopropanation, X-H insertion is the preferred pathway for diazo decomposition. Our preliminary data supported this conclusion, as for all substrates the X-H insertion product was the only isolated product. We also wondered whether there was an inherent trend of reactivity within different X-H bonds and carried out additional competition studies (Scheme 3.12). Interestingly, when diazo **3.4** was treated with equal amount of aniline and phenol (one equivalent each), only aniline insertion product **3.38** was formed. In another case, *n*-butyl alcohol was a superior substrate compared to acetamide. These results indicate that selective X-H insertion in the presence of multiple X-H bonds is viable.



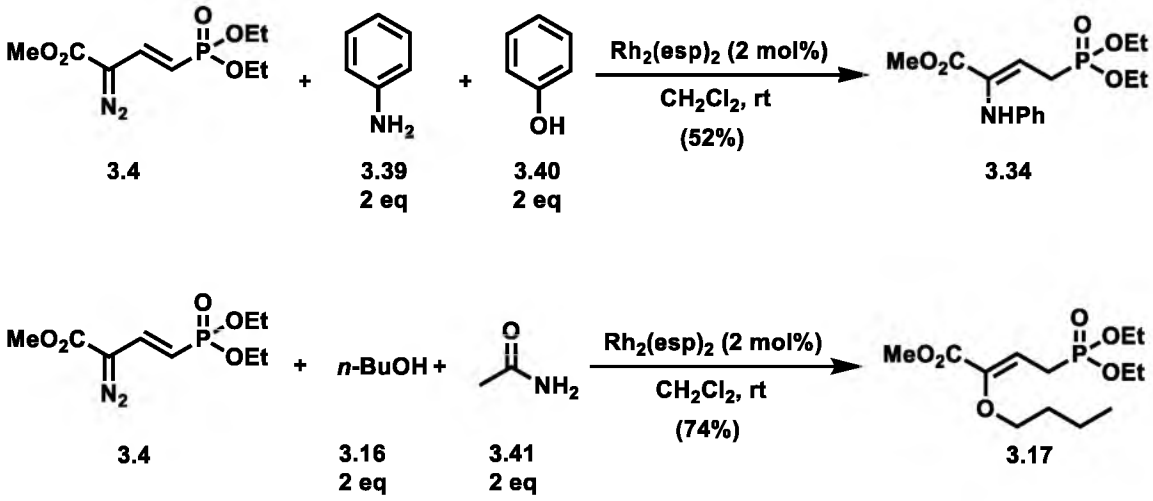
Scheme 3.9 Unsuccessful O-H insertion of tertiary alcohol



Scheme 3.10 N-H insertion: substrate scope



Scheme 3.11 S-H insertion of thiophenol



Scheme 3.12 Competition study

3.3 Intramolecular Cyclizations of the O-H insertion products

3.3.1 Introduction

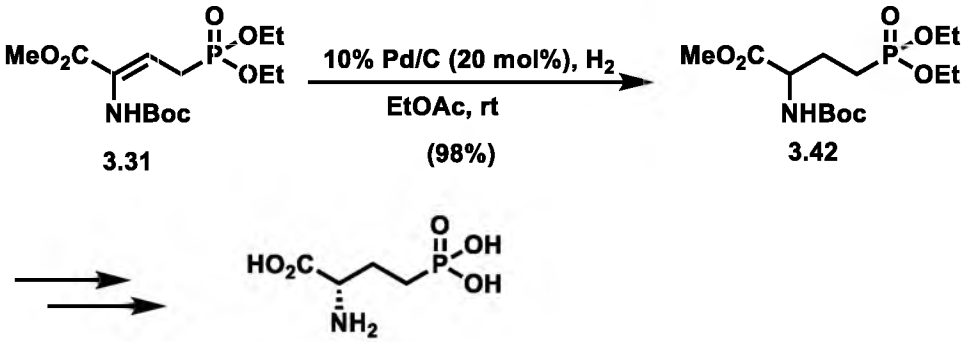
We have successfully demonstrated that X-H insertion reaction of diazo vinyl phosphonates can serve as a convenient and efficient tool for the stereoselective construction of enol ethers, enamines and vinyl sulfides. One straightforward target was L-2-amino-4-phosphonobutanoic acid (L-AP4).[6] L-AP4 has been shown to be a potent Group III metabotropic glutamate receptor agonist. Presumably, reduced product **3.42** could serve as a precursor to form L-AP4 through functional group manipulations (Scheme 3.13).

We envisioned that subsequent transformations on the insertion products could be carried out in order to further amplify their synthetic utility. The synthesis of heterocycles such as furans and oxetanes by intramolecular cyclizations of similar α-alkoxy esters has been reported by the Fujisawa and Bull groups, respectively (Scheme 3.14).[7]

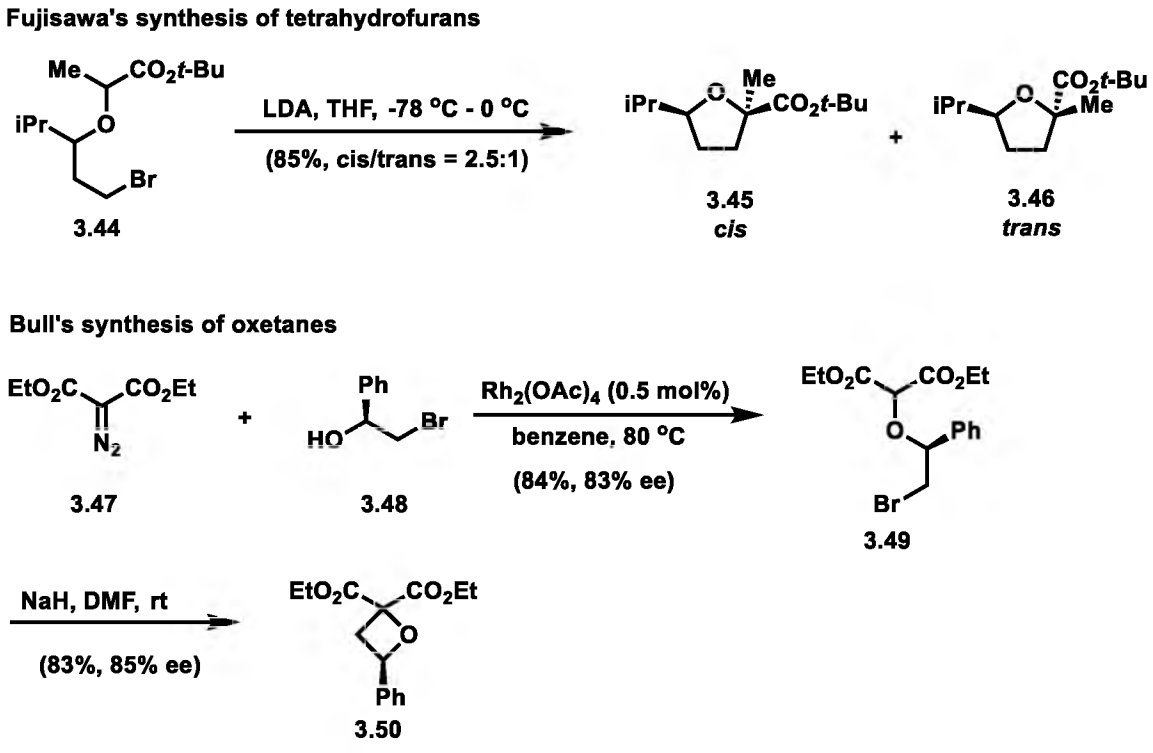
We believe that the phosphonocrotonate system is facile to base deprotonation and provides a very good nucleophile. In particular, it will react with a tethered electrophile to form heterocycles (Scheme 3.15). Since the anion of the phosphonocrotonate can reside at either of the two positions as shown in **3.52** and **3.54**, it would be interesting to see which anion is the preferred reactive species in the cyclizations.

3.3.2 Synthesis of dihydrofurans via cyclization of propargyl vinyl ethers

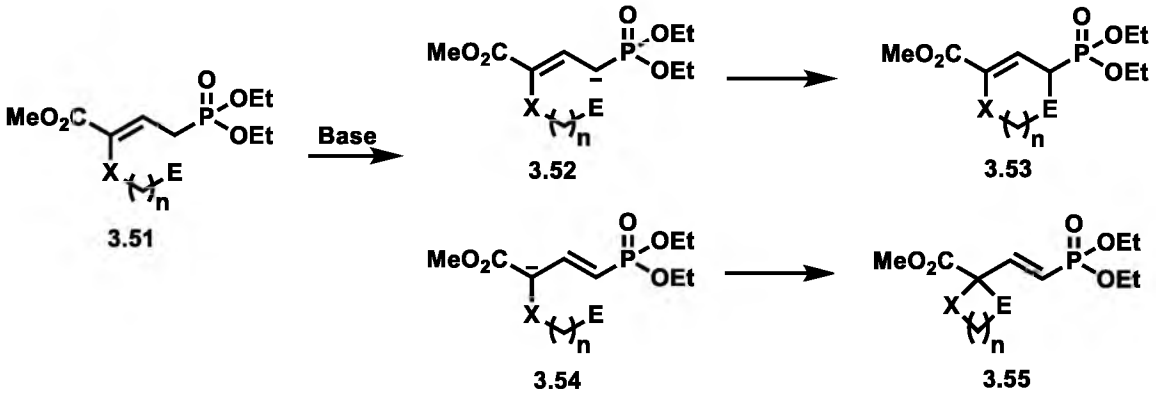
Although we planned to test the intramolecular cyclization, the first piece of useful information came from an unexpected result. We previously demonstrated that allyl substrates **3.19** underwent Claisen rearrangement under thermal conditions and α-ketoester **3.56** was formed (Scheme 3.16). When we tried to apply the same conditions to a similar propargyl substrate **3.21** in hope of obtaining the corresponding allenyl α-ketoester, only a complex mixture was formed. The Kirsch group have reported that when treating **3.57** with silver triflate and DBU, pyran **3.58** was formed via a Claisen rearrangement-6π electrocyclization cascade mechanism (Scheme 3.17).[8] When these conditions were applied to **3.21**, to our surprise, dihydrofuran **3.61** was formed in 91% yield.



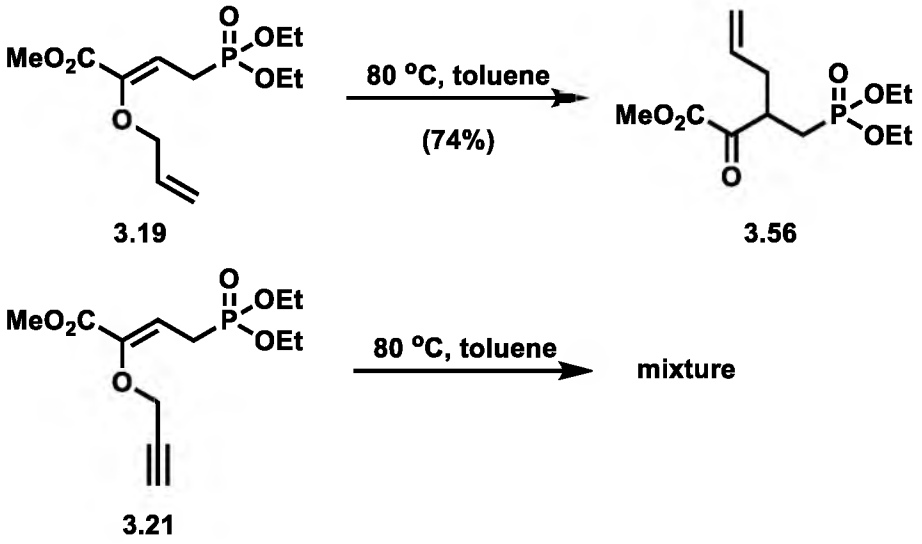
Scheme 3.13 Synthetic efforts towards L-AP4



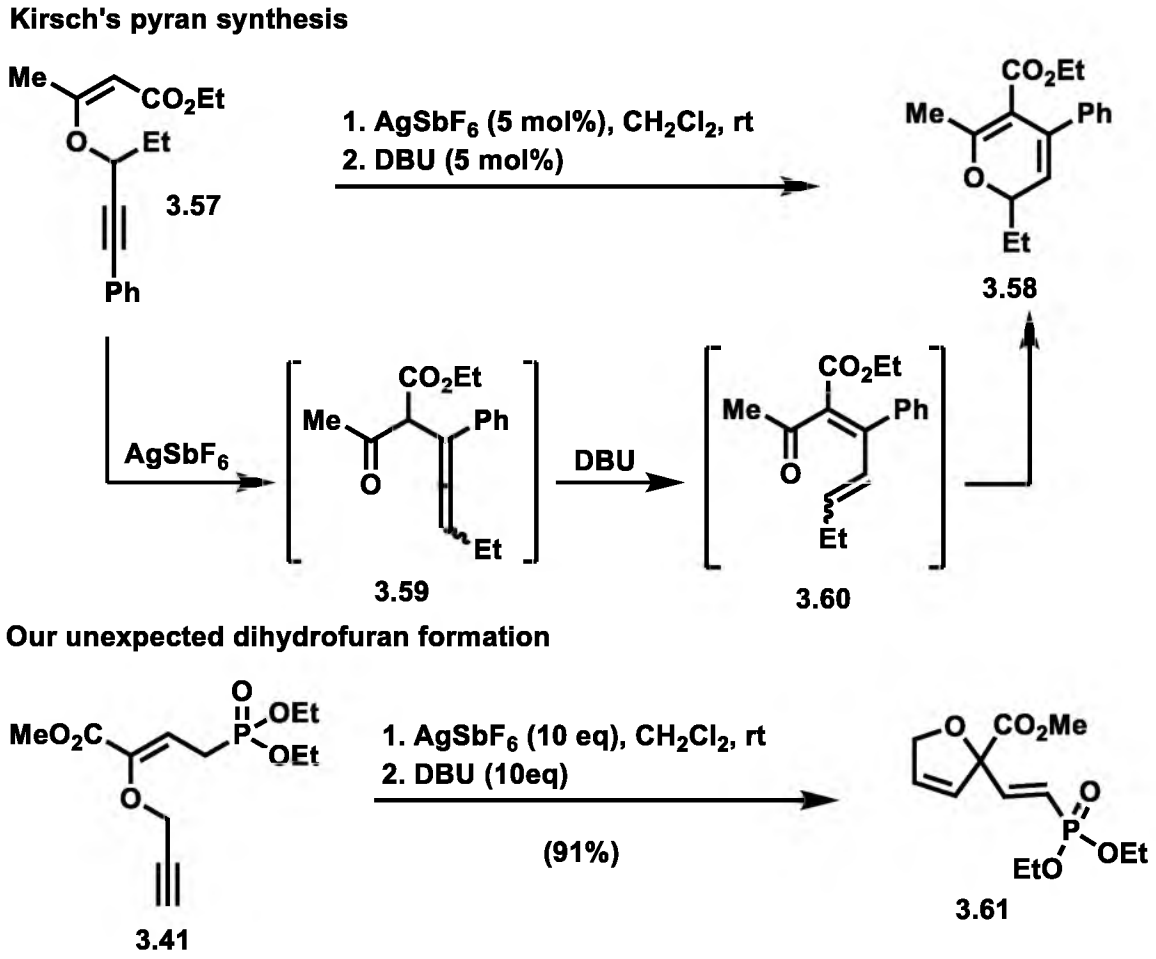
Scheme 3.14 Cyclization for tetrahydrofuran and oxetane formation



Scheme 3.15 Proposed cyclization pathway



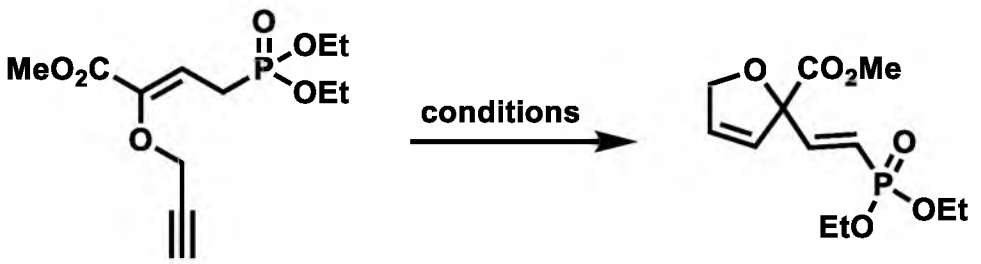
Scheme 3.16 Claisen rearrangement



Scheme 3.17 Cyclization with $AgSbF_6$/DBU

The reaction conditions to form **3.61** were further optimized (Table 3.1). Although cyclization with $ZnCl_2$ was unproductive, the $AgSbF_6$ catalyst could be replaced by the less expensive and more robust $AgNO_3$ catalyst. Utilization of a stronger base such as *t*-BuOK led to diminished yield presumably due to decomposition. Acetone proved to be a superior solvent for this reaction in terms of reaction rate and yield. A catalytic amount of DBU could be used, but the reaction rate decreased dramatically.

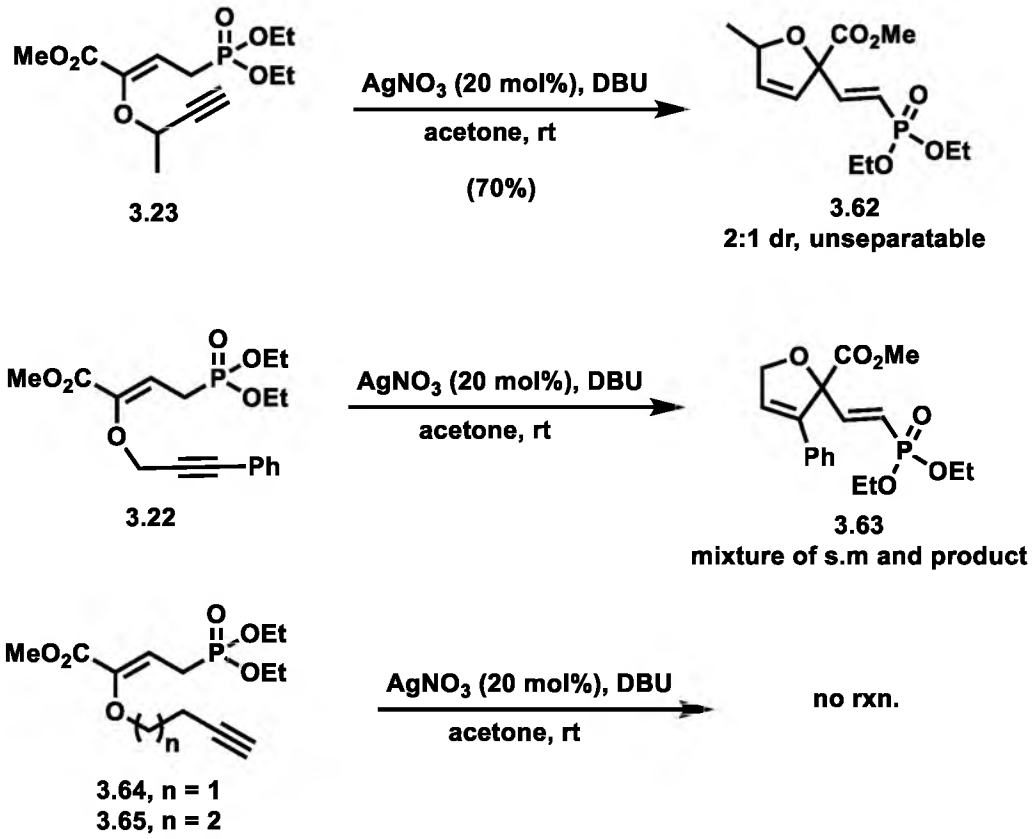
Table 3.1 Optimization of propargyl vinyl ether cyclization



3.41 **3.61**

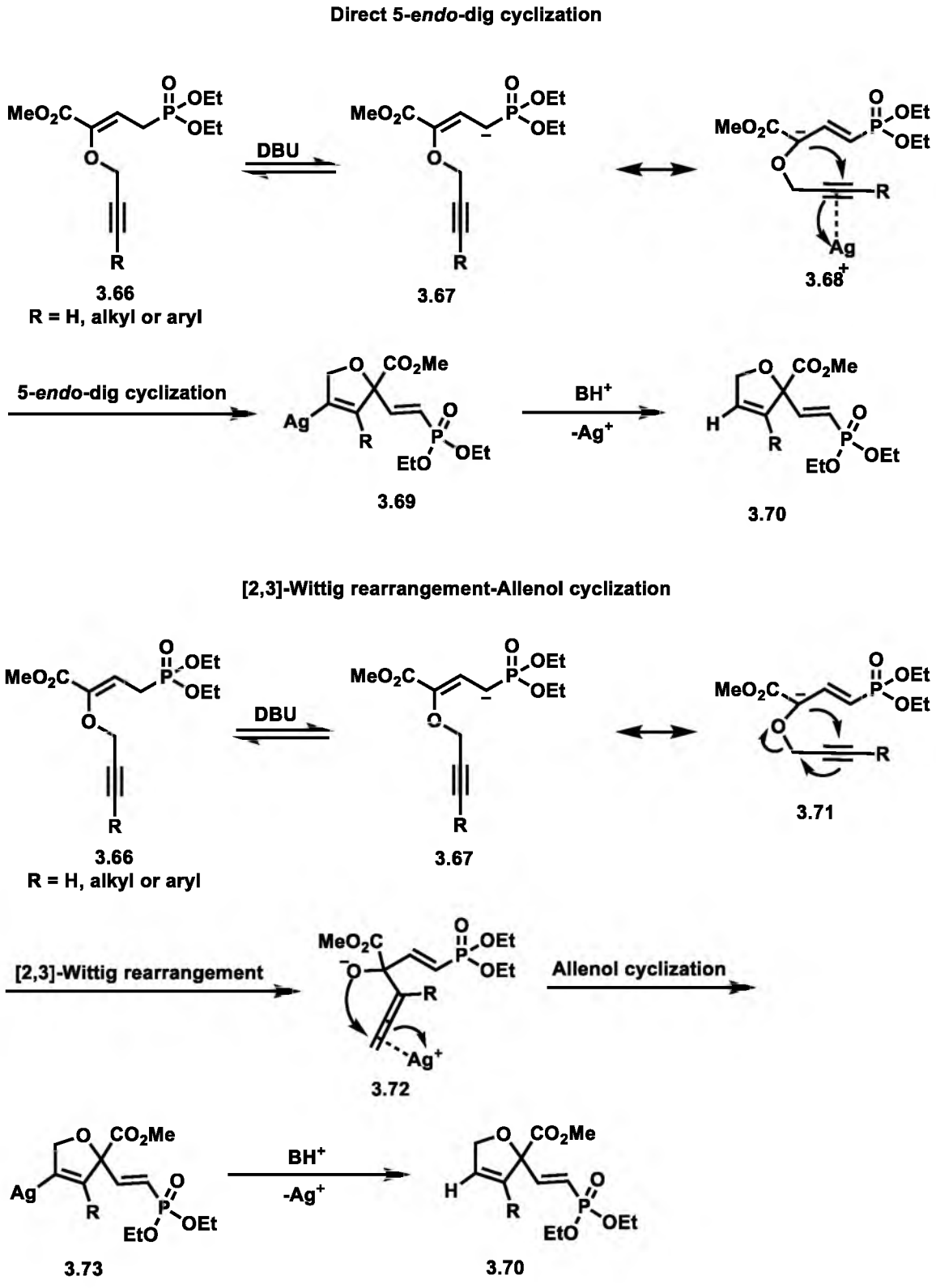
entry	Lewis acid (eq)	base (eq)	solvent	temp	time	yield
1	$AgSbF_6$ (10)	DBU (10)	CH_2Cl_2	rt	2h	83%
2	$ZnCl_2$ (0.2)	DBU (1.2)	CH_2Cl_2	rt	16h	n. a.
3	$AgNO_3$ (0.2)	DBU (1.2)	CH_2Cl_2	rt	24h	71%
4	$AgNO_3$ (0.2)	*t*-BuOK (1.2)	CH_2Cl_2	rt	1h	36%
5	$AgNO_3$ (0.2)	DBU (1.2)	acetone	rt	2h	91%
6	$AgNO_3$ (0.2)	DBU (0.4)	acetone	rt	10h	94%
7	$AgNO_3$ (0.2)	DBU (0.2)	acetone	rt	16h	91%
8	none	*t*-BuOK (1.2)	CH_2Cl_2	rt	5 min	24%
9	none	DBU (2)	THF	70°C	8h	55%

We then decided to explore the substrate scope of this reaction (Scheme 3.18). Secondary propargyl substrate **3.23** participated in the cyclization smoothly. However, only an inseparable 2:1 mixture of diastereomers was formed. Reaction of terminal substituted propargyl substrates such as **3.22** resulted in an inseparable mixture of starting material and desired product. Similar cyclizations didn't occur with homopropargyl substrate **3.64** or bis-homopropargyl substrate **3.65**.



Scheme 3.18 Cyclization of propargyl vinyl ether: substrate scope

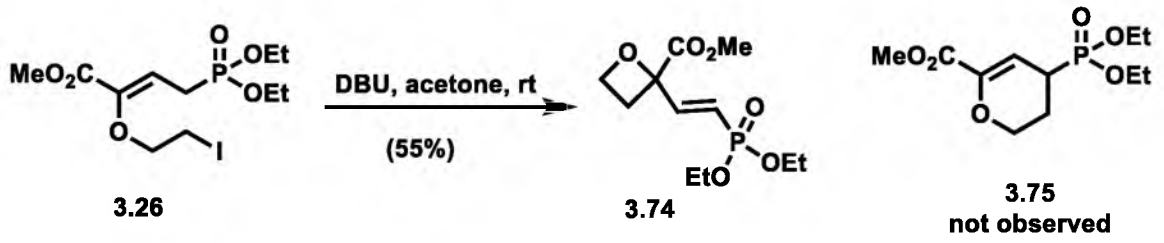
Two plausible mechanisms have been proposed for this reaction (Scheme 3.19). Direct 5-*endo*-dig cyclization of the transient anion **3.68** with the help of the silver salt seems feasible. Another possible pathway would involve a Wittig rearrangement followed by an intramolecular cyclization of the allenol intermediate **3.72**. Because similar Wittig rearrangements normally require a stoichiometric amount of strong base, we believe the direct 5-endo-dig mechanism is more likely.[9] To the best of our knowledge similar cyclizations of propargyl vinyl ethers have never been reported. This mechanism could also explain the incomplete cyclization of substrate **3.22** as the bulky phenyl group prevents the transient anion **2.150** to attack the alkyne.



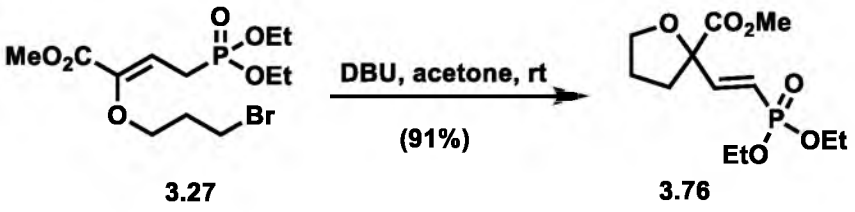
Scheme 3.19 Two plausible mechanism for propargyl vinyl ether cyclization

3.3.3 Synthesis of oxetanes and tetrahydrofurans

We have successfully demonstrated that the intramolecular cyclization of propargyl vinyl ethers give dihydrofurans. An alternative cyclization strategy is employing halide substrates such as **3.26** and **3.27** in an S_N2 fashion. We were pleased to find that treatment of **3.26** with DBU gave **3.74** in the absence of a silver catalyst (Scheme 3.20). This result was quite unexpected, because we initially speculated that the seemingly more stable pyran **3.75** would be the preferred product. Bromide **3.27** was then exposed to the same reaction to give tetrahydrofuran **3.76** in good yield (Scheme 3.21). It's worth noting that furan formation was more rapid (6 h vs 18 h) and efficient (yield 91% vs 55%) than oxetane formation.



Scheme 3.20 Oxetane formation via 4-exo-tert cyclization

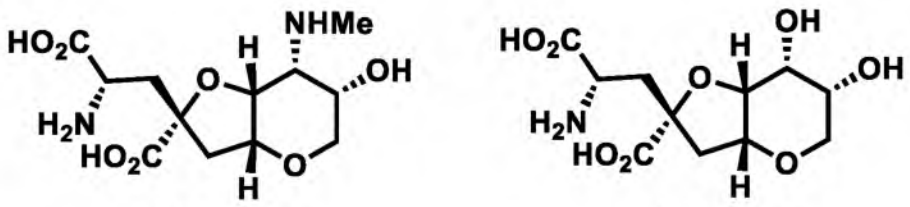


Scheme 3.21 Tetrahydrofuran formation via 5-exo-tert cyclization

3.4 Efforts towards the synthesis of dysiherbaine analogs

3.4.1 Introduction

Natural products containing a tetrahydrofuran motif are abundant in nature. We became particularly interested in the dysiherbaine family of natural products and their analogs (Scheme 3.22). Dysiherbaine was first isolated in 1997 by the Sakai group from the marine Micronesian sponge *Dysidea herbacea*.[10] The structure of dysiherbaine is quite intriguing: it contains a unique cis-fused hexahydrofuro[3,2,*b*] pyran backbone which is most likely derived from carbohydrate with a pedant amino acid (glutamate). In addition to its structure, neuropharmacological studies also revealed that this compound is a highly selective agonist towards the kainate (KA) subclass of ionotropic glutamate receptors.[11] More detailed experiments indicated that dysiherbaine and its analogs preferred to bind kainate subtype GluK1 and to some extent GluK2. It has been shown that antagonists of GluK1 are effective towards diseases such as epilepsy and neurodegeneration.[11] Neodysiherbaine showed a similar neurological profile but with a decreased binding affinity.[12]



3.77
dysiherbaine

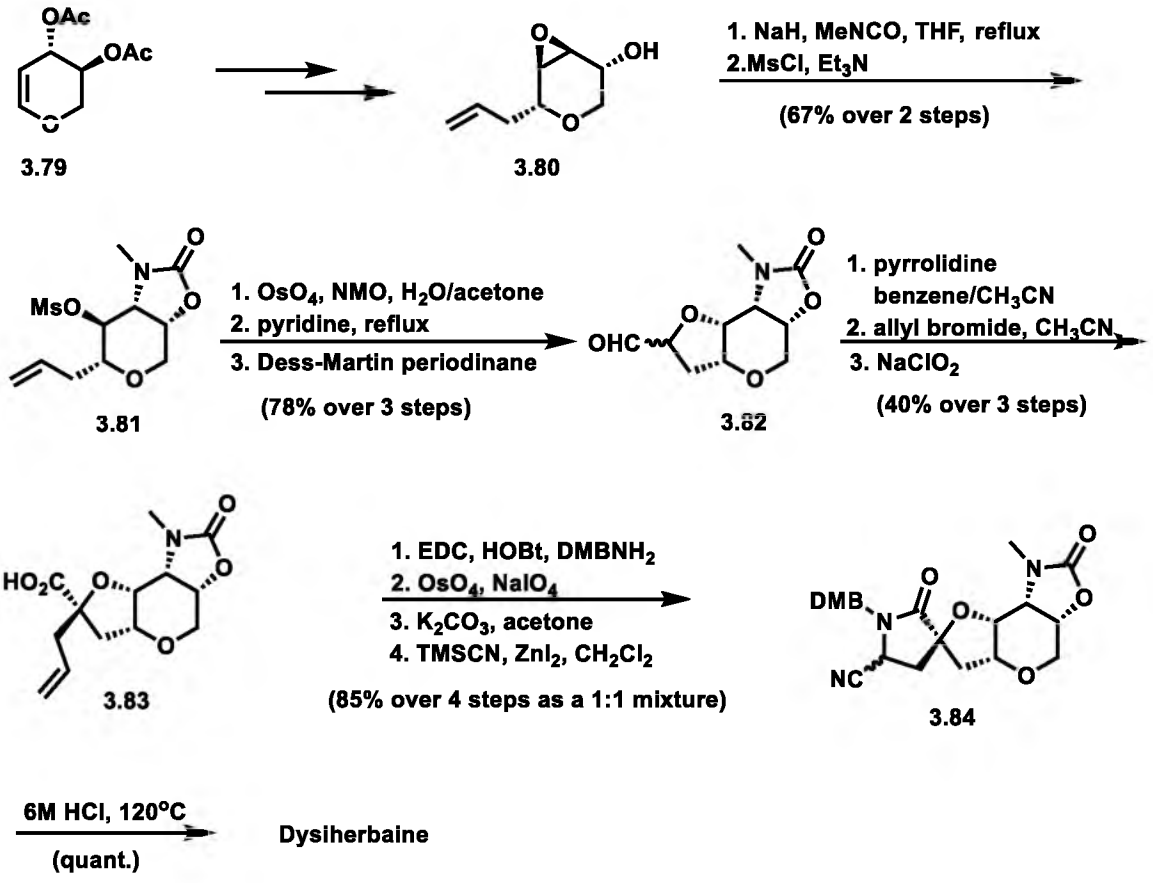
3.78
neodysiherbaine

Scheme 3.22 Dysiherbaine family natural products

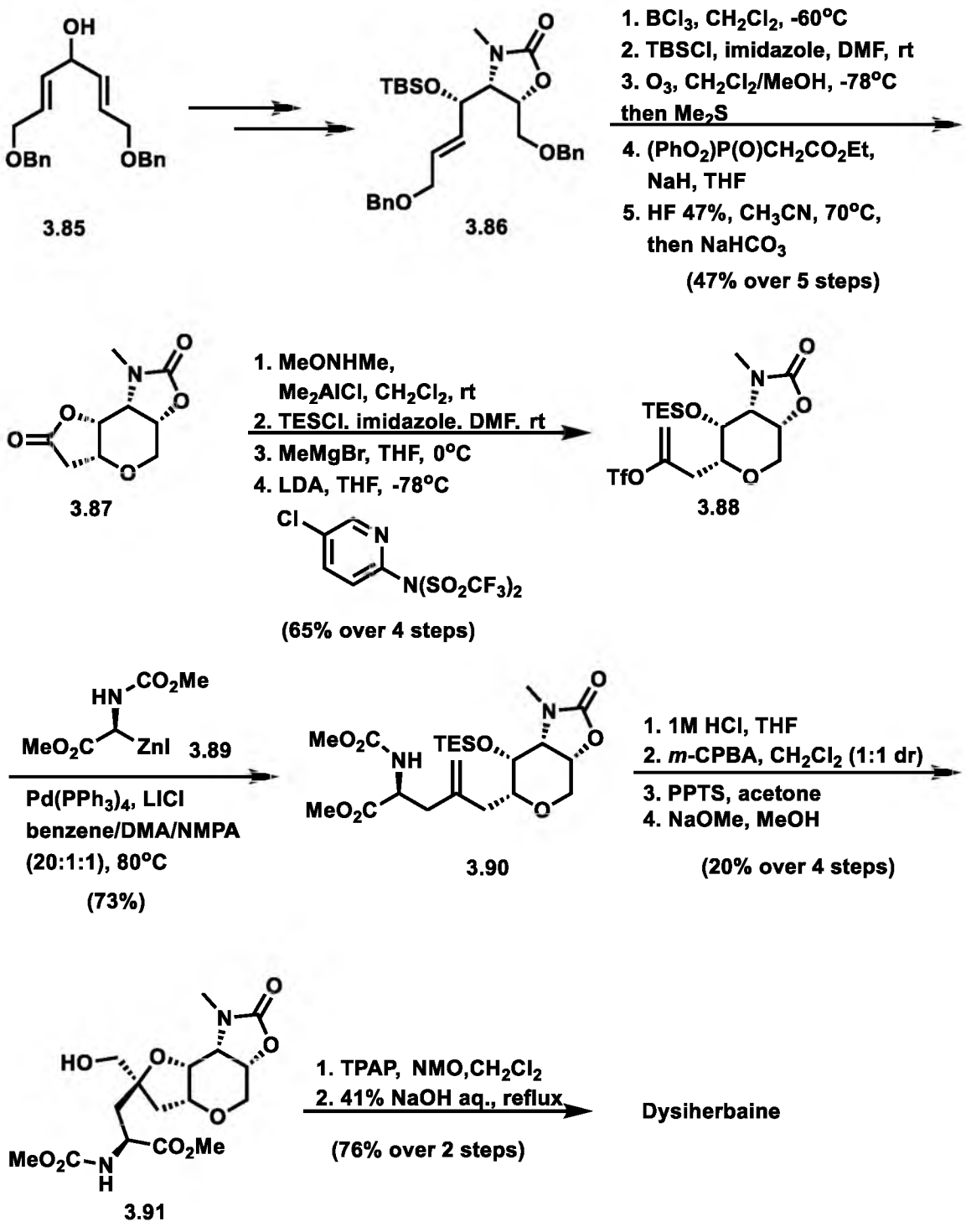
Several total syntheses of dysiherbaine have been accomplished. The first total synthesis of dysiherbaine was completed by the Snider group in 2000 (Scheme 3.23).[13] Starting from xylose derivative **3.79**, the C8-C9 stereochemistry was secured by reacting epoxide **3.80** with methyl isocyanate. The tetrahydrofuran ring in **3.82** was formed by an S_N2 displacement of the mesylate in **3.81**. While the alkylation of **3.82** with allyl bromide provided the desired stereochemistry at the C4 position, installation of the amino acid moiety gave only a 1:1 mixture of diastereomers of **3.84**. Global deprotection provided the natural product from **3.79** in 17 steps.

The Hatakeyama group applied a compeletely different strategy in their total synthesis (Scheme 3.24).[14] Starting from an achiral linear material **3.85**, the absolute stereochemistry of C7 to C9 was introduced with a series of enantio- and diastereoselective transformations. The pyran ring in **3.87** was formed by an intramolecular Michael addition. Vinyl triflate **3.88** was then synthesized and coupled with enantioenriched zinc reagent **3.89** to form **3.90**. The tetrahydrofuran ring was formed by a base promoted ring opening reaction of epoxide. Overall dysiherbaine was synthesized from **3.85** in 24 steps.

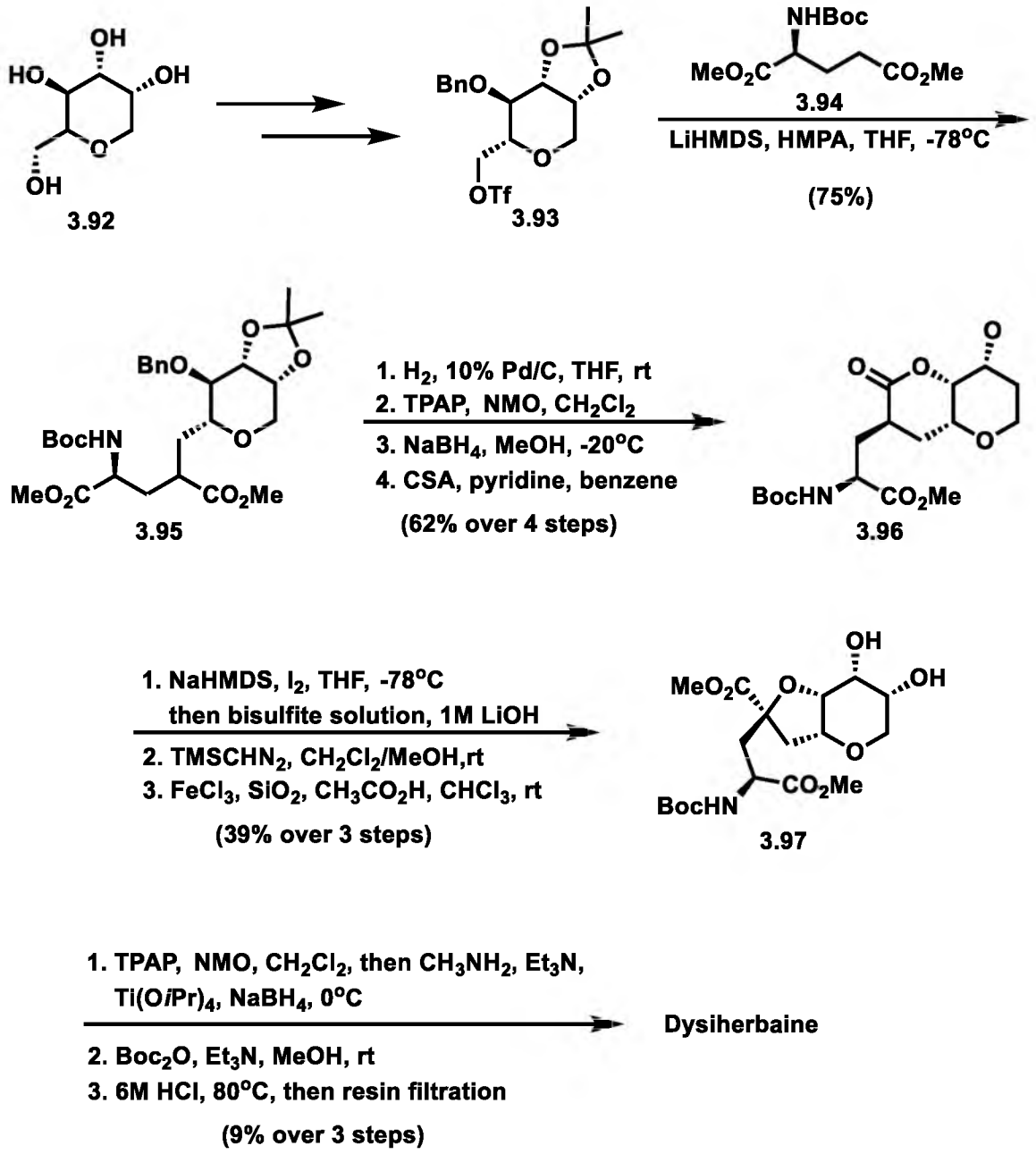
Chamberlin's synthesis of dysiherbaine started with D-mannose derivative **3.92**. The coupling of glutamic acid **3.94** with triflate **3.93** produced the requisite pyran **3.95** (Scheme 3.25).[15] The tetrahydrofuran ring was generated using a Fleet ring contraction reaction. The C8 methylamino group was installed at a late stage by reductive amination. Dysiherbaine was synthesized from **3.92** in 15 steps.



Scheme 3.23 Snider's total synthesis of Dysiherbaine



Scheme 3.24 Hatakeyama's total synthesis of Dysiherbaine

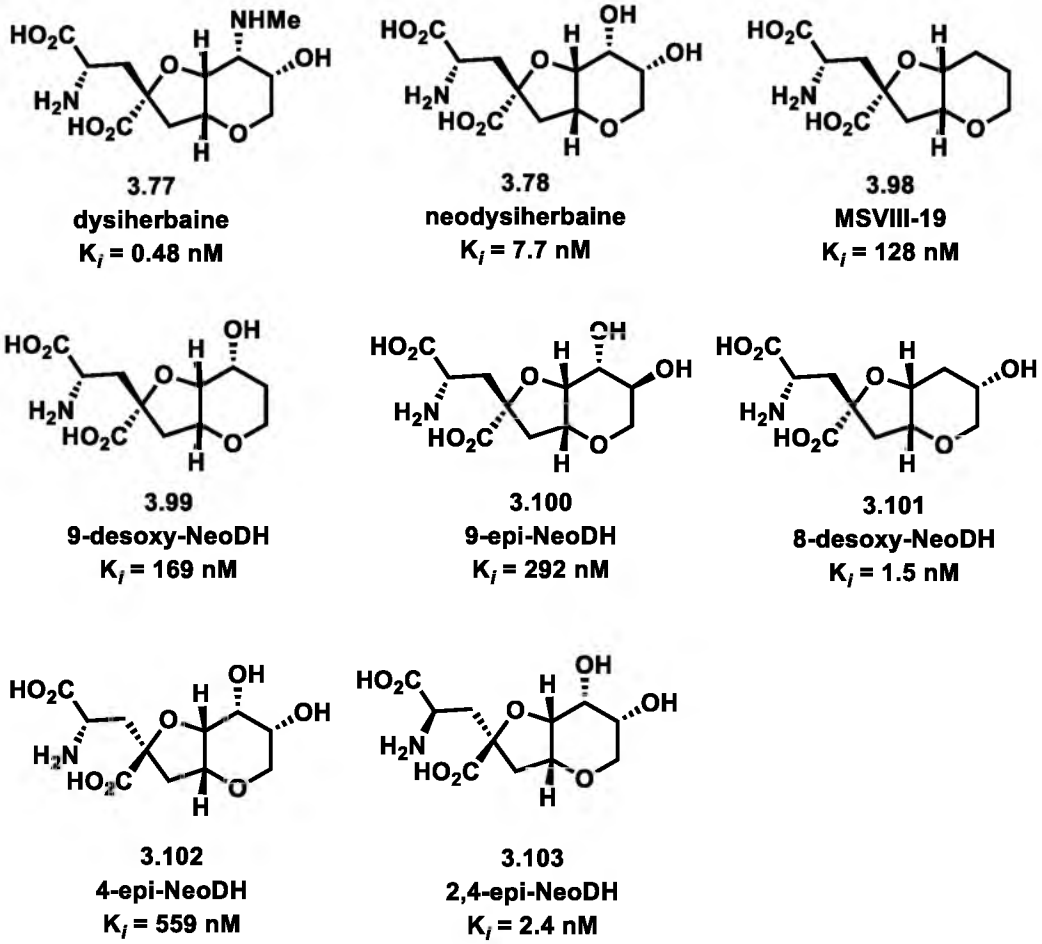


Scheme 3.25 Chamberlin's total synthesis of Dysiherbaine

3.4.2 Synthesis of dysiherbaine analogs

Because of their notable neuro-activity, analogs of dysiherbaine have been synthesized in order to understand their structure-activity relationship (SAR) with glutamate receptors.[16] Modifications at different positions on the dysiherbaine skeleton have been accomplished (Scheme 3.26). Interestingly, dysiherbaine analog MSVIII-19 without the C8 or C9 substitution was identified as the first known antagonist for GluK1.[17] The C9 hydroxy group is important for binding with GluK1, because either loss of the C9 substituent or epimerization of it as in compound **3.99** and **3.100** resulted in greatly decreased binding affinity.[18] The C8 substitution affects the binding less dramatically as compound **3.101** maintained similar binding affinity as neodysiherbaine. The C4 epimer of neodysiherbaine **3.102** lost its affinity significantly; interestingly, bis-C2, C4 epimer **3.103** restored the binding affinity and was an antagonist against GluK1.[19]

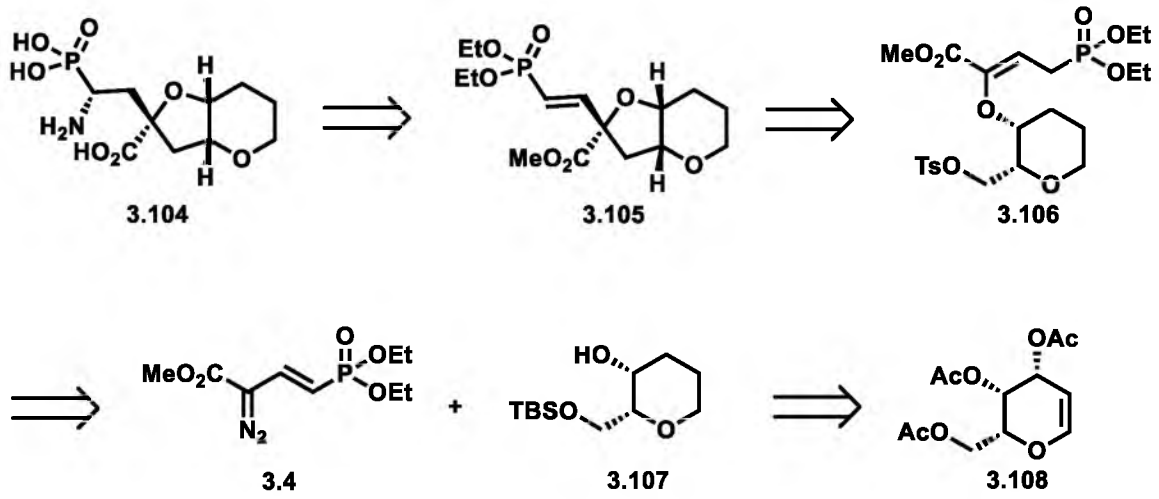
α-Amino phosphonic acids can be structural mimics of α-amino acids and have shown promising applications in medicinal chemistry.[20] We envisioned that the phosphonic acid analog **3.104** of MSVIII-19 which has never been reported before can be accessible from our O-H insertion-cyclization approach, as shown in Scheme 3.27. The target molecule would be derived from phosphonate **3.105**, which would be formed by an intramolecular cyclization of tosylate **3.106**. At the outset we were not sure about the stereochemistry of the C4 carbon after the cyclization but we hoped that both C4 diastereomers could bring us useful information for the SAR study. The tosylate would be synthesized from an O-H insertion of the diazo vinyl phosphonate **3.4** and the requisite alcohol **3.107**.



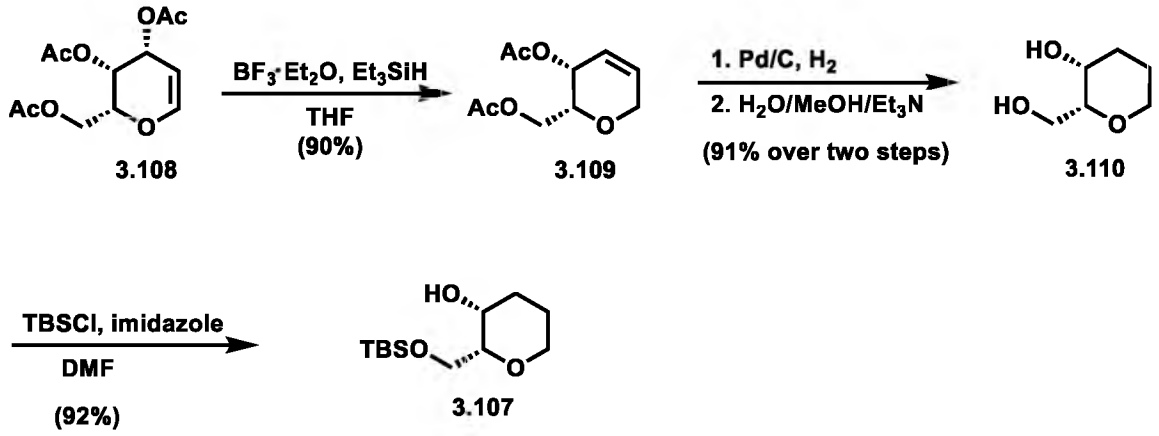
Scheme 3.26 Analogs of Dysiherbaine

Compound **3.107** could be realized from commercially available galactose derivative **3.108**.

With the aforementioned retrosynthetic analysis in mind, we set out to synthesize alcohol **3.107** first (Scheme 3.28). Treating compound **3.108** with Ferrier rearrangement condition readily provided alkene **3.109**. Subsequent hydrogenation and deprotection resulted in diol **3.110**. The primary alcohol was selectively protected as the corresponding TBS ether to give the alcohol precursor **3.107** for O-H insertion.

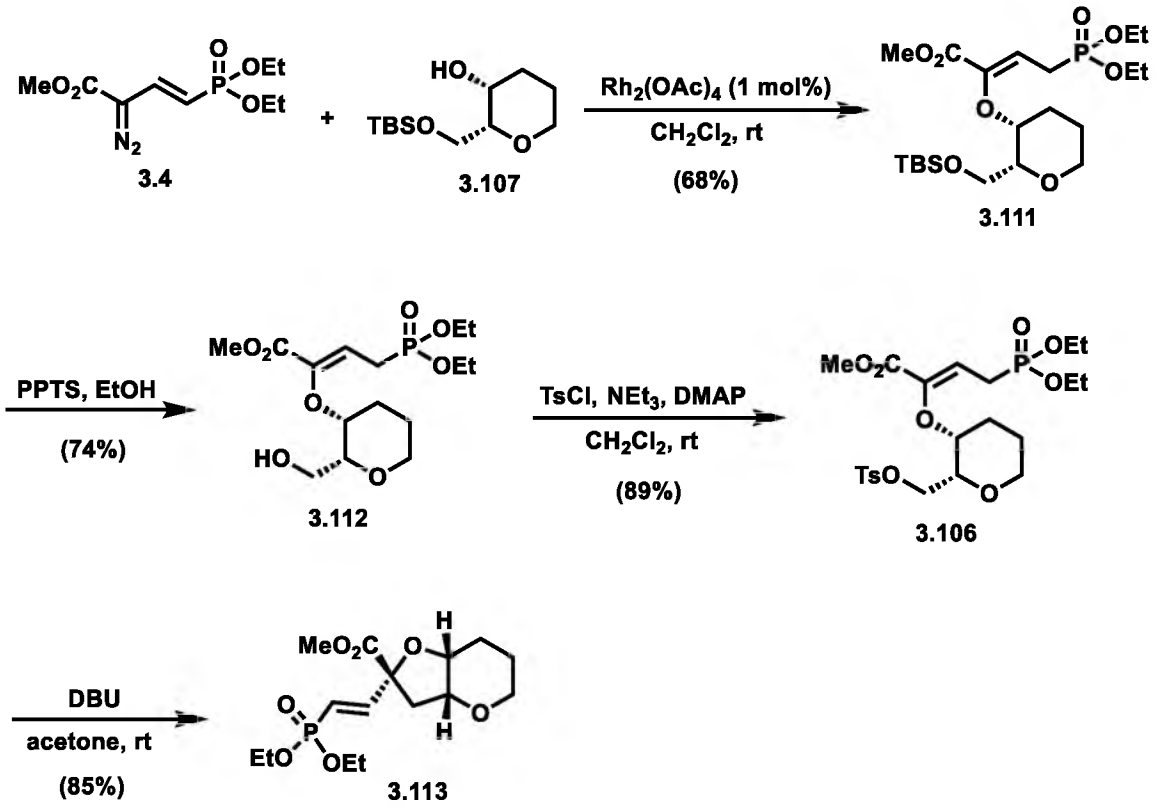


Scheme 3.27 Retrosynthetic analysis of phosphonic acid analog



Scheme 3.28 Synthesis of alcohol precursor

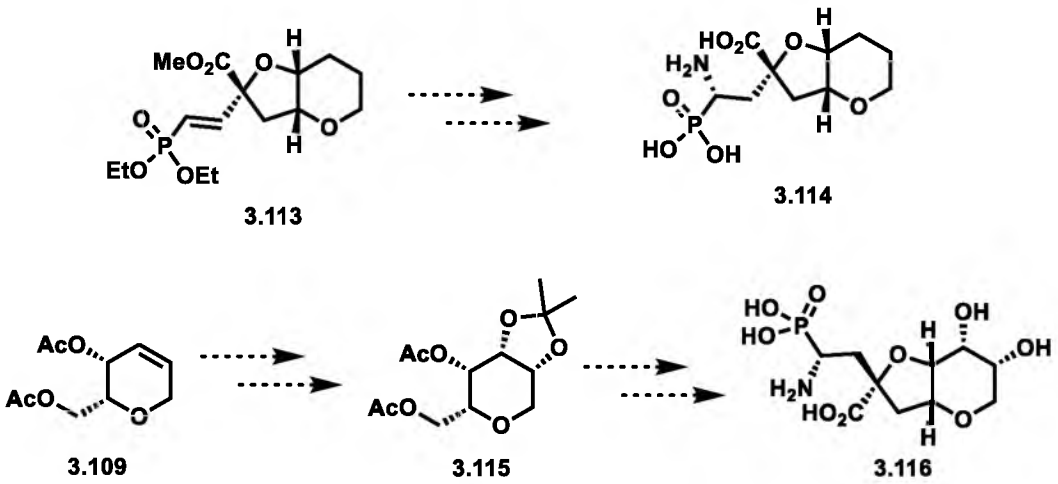
To our delight, the key O-H insertion reaction between diazo **3.4** and alcohol **3.107** went smoothly and gave the desired insertion product **3.111** in 68% yield (Scheme 3.29). Removal of the TBS group provided the primary alcohol in 74% yield, which upon treating with TsCl and DMAP gave the corresponding tosylate **3.106** in 89% yield. The stage now was set for the cyclization. When treating the tosylate **3.106** with DBU in acetone, a single diastereomer **3.113** was formed in



Scheme 3.29 Synthesis of phosphonate analog

85% yield. NOE experiments revealed that the stereochemistry of the C-4 carbon was actually opposite to the the C-4 stereochemistry in the natural product dysiherbaine.

We are currently working on the rationalization of the stereo outcome of the cyclization. Because the 2,4-epi-NeoDH **3.103** showed strong binding affinity while 2-epi-NeoDH **3.102** only weakly binds to GluK1, in the next stage we plan to aim for the 2,4-epimer of the phosphonic acid analog **3.114** (Scheme 3.30). Since the C-9 substitution is proved to be important for binding affinity, we also intend to synthesize analog **3.116** bearing a key C-9 substitution.



Scheme 3.30 Future work

3.5 Conclusion

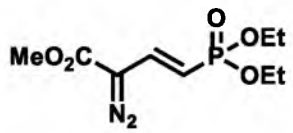
Diazo vinyl phosphonate **3.4** participated in stereoselective X-H insertion reactions to give enol ethers, enamines and vinyl sulfides. Subsequent cyclization of O-H insertion products provided a rapid access to dihydrofurans, oxetanes and tetrahydrofurans. Notably, the O-H insertion/cyclization strategy was applied to the synthesis of dysiherbaine analogs.

Future work will focus on exploring new reactivity of this novel diazo vinyl phosphonate. Currently, the possibility of conjugating the phosphonate onto iron nanoparticles is under investigation in our group. The synthesis of other phosphonate analogs of dysiherbaine is another direction we will pursue.

3.6 Experimental

NMR spectra were recorded on a Varian Unity-300, Varian Inova-400 or a Varian VXR-500 spectrometer. Chemical shifts were reported in δ, parts per

million (ppm), relative to chloroform (7.25) or dichloromethane (5.29) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Armarego. W. L. F. and Chai, C. L. L., Oxford, 2009). Spectroscopic grade CH_3CN was stored over activated 4Å molecular sieves and used without additional purification. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of dried nitrogen in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

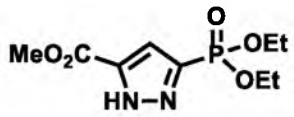


3.4

Methyl-*E*-2-diazo-4-(diethoxyphosphoryl)but-3-enoate (3.4). To a solution of **3.1** (0.236 g, 1.0 mmol) and tosyl azide (0.236 g, 1.2 mmol) in THF (8 mL) at 0 °C was added DBU (0.18 mL, 1.2 mmol) dropwise. The resulting mixture was warmed to rt slowly and allowed to stir for 8 h. Concentration and flash chromatography (1:2 hexanes:ethyl acetate) provided 0.206 g of diazo vinyl phosphonate **3.4** (80%) as a pale yellow oil.

3.4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 22.5, 17.6 Hz, 1H), 5.50 (dd, *J* = 16.1, 16.1 Hz, 1H), 4.10 - 4.02 (m, 4H), 3.82 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 6H); ^{13}C

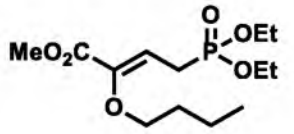
NMR (125 MHz, $CDCl_3$) δ 163.7, 134.6 (d, *J* = 11.5 Hz), 107.1 (d, *J* = 197.6 Hz), 62.1 (d, *J* = 7.9 Hz), 52.7, 16.6 (d, *J* = 7.9 Hz); IR (neat) 2983, 2916, 2114, 1709, 1602, 1439, 1337, 1244, 1217, 1051, 1025, 962 cm^{-1}; LRMS *m/z* calcd for $C_9H_{16}N_2O_5P$ $[M+H]^+$ 263.1, found 263.2.



3.6

Methyl 3-(diethoxyphosphoryl)-*1H*-pyrazole-5-carboxylate (3.6). A solution of diazo **3.4** 29 mg (0.11 mmol) in toluene (3 ml) was heated at 80 °C for 12 h. Concentration and flash chromatography (1:5 hexanes/ethyl acetate) gave 21 mg of **3.6** (71%) as a colorless oil.

3.6: ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 2.2 Hz, 1H), 4.21 - 4.02 (m, 4H), 3.87 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 142.7, 134.5 (d, *J* = 228.1 Hz), 114.7 (d, *J* = 19.1 Hz), 63.6 (d, *J* = 5.5 Hz), 52.4, 16.3 (d, *J* = 6.6 Hz); IR (neat) 3128, 3053, 2983, 1732, 1457, 1365, 1225, 1174, 1051, 1017, 977 cm^{-1}; LRMS *m/z* calcd for $C_9H_{16}N_2O_5P$ $[M+H]^+$ 263.1, found 363.1



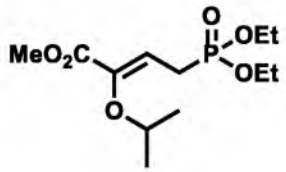
3.17

Methyl-*Z*-2-butoxy-4-(diethoxyphosphoryl)but-2-enoate (3.17). Representative procedure for O-H, N-H and S-H insertion reactions of diazo vinyl phosphonate **3.4**:

The generation of butyl enol ether **3.17**: To a solution of **3.4** (0.026 g, 0.099 mmol) and butanol (0.018 mL, 0.20 mmol) in CH_2Cl_2 (3 mL) at rt was added

$Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol) in a single portion. The resulting green mixture was allowed to stir at rt for 4 h. Concentration and flash chromatography (1:1 hexanes:ethyl acetate, SiO_2 was neutralized with 1% NEt_3) provided 25 mg of enol ether **3/17** (82%) as a colorless oil.

3.17: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (dt, *J* = 7.5, 7.5 Hz, 1H), 4.14 - 4.03 (m, 4H), 3.81 (t, *J* = 6.9 Hz, 2H), 3.74 (s, 3H), 2.77 (dd, *J* = 22.4, 7.8 Hz, 2H); 1.64 (pentet, *J* = 6.8 Hz, 2H), 1.41 (sextet, *J* = 7.4 Hz, 2H), 1.29 (t, *J* = 6.8 Hz, 6H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (d, *J* = 3.1 Hz), 147.6 (d, *J* = 13.7 Hz), 117.1 (d, *J* = 10.6 Hz), 72.6 (d, *J* = 2.3 Hz), 62.3 (d, *J* = 6.1 Hz), 52.2, 32.2, 24.5 (d, *J* = 140.4 Hz), 19.3, 16.6 (d, *J* = 6.1 Hz), 14.0; IR (neat) 2958, 1727, 1650, 1437, 1252, 1164, 1107, 1024, 963 cm^{-1}; LRMS *m/z* calcd for $C_{13}H_{26}O_6P$ 309.1 $[M+H]^+$, found 309.3.

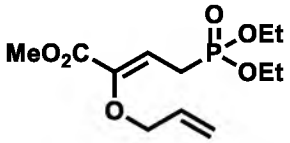


3.18

Methyl-*Z*-4-(diethoxyphosphoryl)-2-isopropoxybut-2-enoate (3.18). Enol ether was prepared according to the procedure given for the formation of **3.17** using 0.025 g (0.095 mmol) of **3.4**, 0.015 mL (0.19 mmol) of isopropyl alcohol and 0.8 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 23 mg of **3.18** (82%) as colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.18: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 7.8, 7.8 Hz, 1H), 4.28 (septet, *J* = 5.9 Hz, 1H), 4.14 - 4.04 (m, 4H), 3.74 (s, 3H), 2.78 (dd, *J* = 22.5, 8.3 Hz, 2H),

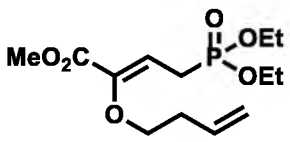
1.29 (t, *J* = 7.3 Hz, 6H), 1.21 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1 (d, *J* = 2.3 Hz), 146.2 (d, *J* = 14.6 Hz), 117.4 (d, *J* = 10.7 Hz), 74.2 (d, *J* = 2.3 Hz), 62.3 (d, *J* = 6.1 Hz), 52.2, 24.6 (d, *J* = 141.2 Hz), 22.6, 16.6 (d, *J* = 6.1 Hz); IR (neat) 3020, 2981, 1724, 1647, 1437, 1265, 1249, 1193, 1024, 964 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{24}O_6P$ 295.2 $[M+H]^+$, found 295.3.



3.19

Methyl-*Z*-2-(allyloxy)-4-(diethoxyphosphoryl)but-2-enoate (3.19). Allyl enol ether **3.19** was prepared according to the procedure given for the formation of **3.17** using 0.026 g (0.099 mmol) of **3.4**, 0.014 mL (0.20 mmol) of prop-2-en-1-ol and 0.9 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 24 mg of **3.19** (83%) as colorless oil after flash chromatography (1:1 hexanes/ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

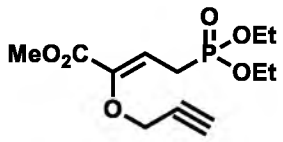
3.19: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 7.8, 7.8 Hz, 1H), 5.96 (ddt, *J* = 17.1, 10.8, 5.8 Hz, 1H), 5.32-5.29 (m, 1H), 5.20 (dd, *J* = 11.7, 1.0 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 4.14 - 4.04 (m, 4H), 3.76 (s, 3H), 2.78 (dd, *J* = 22.4, 7.8 Hz, 2H), 1.30 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (d, *J* = 3.1 Hz), 147.1 (d, *J* = 14.5 Hz), 133.6, 118.6, 117.9 (d, *J* = 10.7 Hz), 73.4 (d, *J* = 3.0 Hz), 62.3 (d, *J* = 6.9 Hz), 52.3, 24.6 (d, *J* = 141.2 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2984, 1727, 1651, 1438, 1253, 1046, 1024, 964 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{22}O_6P$ 293.1 $[M+H]^+$, found 293.3



3.20

Methyl-*Z*-2-(but-3-enyloxy)-4-(diethoxyphosphoryl)but-2-enoate (3.20). Homoallyl enol ether **3.20** was prepared according to the procedure given for the formation of **3.17** using 0.025 g (0.095 mmol) of **3.4**, 0.016 mL (0.19 mmol) of but-3-en-1-ol and 0.8 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 24 mg of **3.20** (82%) as a colorless oil after flash chromatography (1:1 hexane:ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.20: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 6.8, 6.8 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.3, 6.3 Hz, 1H), 5.14-5.10 (m, 1H), 5.08-5.04 (m, 1H), 4.14 - 4.04 (m, 4H), 3.89 (t, *J* = 6.3 Hz, 2H), 3.75 (s, 3H), 2.78 (dd, *J* = 22.9, 8.3 Hz, 2H), 2.44-2.40 (m, 2H), 1.30 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (d, *J* = 3.0 Hz), 147.4 (d, *J* = 13.8 Hz), 134.7, 117.6 (d, *J* = 10.6 Hz), 117.3, 71.9 (d, *J* = 3.1 Hz), 62.3 (d, *J* = 6.1 Hz), 52.2, 34.5, 24.6 (d, *J* = 140.4 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2981, 1727, 1653, 1437, 136, 1253, 1165, 1025, 964 cm^{-1}; LRMS m/z calcd for $C_{13}H_{24}O_6P$ 307.1 $[M+H]^+$, found 307.3.

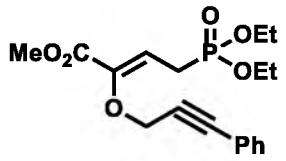


3.21

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(prop-2-yn-1-yloxy)but-2-enoate 3.21. Propargyl enol ether **3.21** was prepared according to the procedure given for the formation of **3.17** using 0.052 g (0.20 mmol) of **3.4**, 0.023 mL (0.40 mmol) of

prop-2-yne-1-ol and 0.8 mg (0.002 mmol) of $Rh_2(OAc)_4$ (0.01 eq) to give 43 mg of **3.21** (74%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.21: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dt, *J* = 7.9, 7.9 Hz, 1H), 4.62 (d, *J* = 2.5 Hz, 2H), 4.14 - 4.04 (m, 4H), 3.76 (s, 3H), 2.87 (dd, *J* = 22.5, 7.9 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H), 1.30 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (d, *J* = 3.1 Hz), 145.6 (d, *J* = 14.5 Hz), 120.0 (d, *J* = 10.7 Hz), 78.7, 76.1, 62.4 (d, *J* = 6.1 Hz), 59.5 (d, *J* = 3.0 Hz), 52.4, 24.9 (d, *J* = 140.4 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 3204, 2983, 1724, 1652, 1438, 1324, 1250, 1106, 1019, 962 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{20}O_6P$ 291.1 $[M+H]^+$, found 291.2.

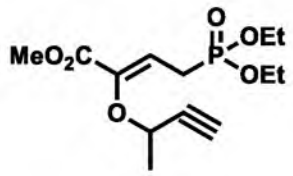


3.22

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(3-phenylprop-2-ynyloxy)but-2-enoate (3.22). Propargyl enol ether **3.22** was prepared according to the general procedure given for the formation of **3.17** using 52 mg (0.20 mmol) of **3.4**, 49 µL (0.40 mmol) of 3-phenyl-2- propyn-1-ol and 0.9 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 58 mg of **3.22** (79%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.22: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.32 - 7.27 (m, 3H), 6.41 (dt, *J* = 7.8, 7.8 Hz, 1H), 4.85 (s, 2H), 4.14 - 4.04 (m, 4H), 3.79 (s, 3H), 2.93 (dd, *J* = 22.5, 7.8 Hz, 2H), 1.28 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, *J* = 2.3 Hz), 145.9 (d, *J* = 13.7 Hz), 131.9, 128.9, 128.6, 122.4, 120.0

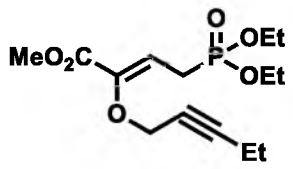
(d, *J* = 10.7 Hz), 87.8, 84.0, 62.4 (d, *J* = 6.2 Hz), 60.4 (d, *J* = 3.8 Hz), 52.4, 24.9 (d, *J* =140.4 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2981, 1724, 1651, 1442, 1251, 1019, 963 cm^{-1}; LRMS m/z calcd for $C_{18}H_{24}O_6P$ 367.1 $[M+H]^+$, found 367.3.



3.23

Methyl-*Z*-2-(but-3-yn-2-yloxy)-4-(diethoxyphosphoryl)but-2-enoate (3.23). Propargyl enol ether **3.23** was prepared according to the general procedure given for the formation of **3.17** using 41 mg (0.16 mmol) of **3.4**, 25 µL (0.31 mmol) of 3-butyn-2-ol and 0.7 mg of $Rh_2(OAc)_4$ (0.002 mmol) to give 33 mg of **3.23** (69%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate. SiO_2 was neutralized with 1% NEt_3).

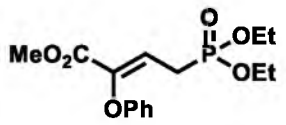
3.23: ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (dt, *J* = 9.2, 6.9 Hz, 1H), 4.94 - 4.90 (m, 1H), 4.14 - 4.04 (m, 4H), 3.76 (s, 3H), 3.08 (ddd, *J* = 20.5, 15.1, 9.3 Hz, 1H), 2.70 (ddd, *J* = 23.9, 15.6, 6.8 Hz, 1H), 2.42 (d, *J* = 2.0 Hz, 1H), 1.55 (d, *J* = 6.2 Hz, 3H), 1.30 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6 (d, *J* = 2.3 Hz), 145.4 (d, *J* = 14.5 Hz), 120.0 (d, *J* = 10.7 Hz), 82.8, 74.4, 67.0 (d, *J* = 2.3 Hz), 62.3 (d, *J* = 2.3 Hz), 62.3 (d, *J* = 2.2 Hz), 52.3, 25.0 (d, *J* = 140.3 Hz), 22.3, 16.6 (d, *J* = 2.2 Hz), 16.6 (d, *J* = 2.2 Hz); IR (neat) 3207, 2985, 1725, 1651, 1252, 1103, 1025, 964 cm^{-1}; LRMS m/z calcd for $C_{13}H_{22}O_6P$ 305.1 $[M+H]^+$, found 305.3.



3.24

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(pent-2-ynyloxy)but-2-enoate (3.24). Propargyl enol ether **3.24** was prepared according to the general procedure given for the formation of **3.17** using 41 mg (0.16 mmol) of **3.4**, 29 µL (0.31 mmol) of 2-pentyn-1-ol and 0.7 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 35 mg (70%) of **3.24** as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.24: ^1H NMR (500 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 8.3, 8.3 Hz, 1H), 4.56 (t, *J* = 2.5 Hz, 2H), 4.14 - 4.04 (m, 4H), 3.75 (s, 3H), 2.86 (dd, *J* = 22.5, 7.8 Hz, 2H), 2.18 (qt, *J* = 7.3, 2.4 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 6H), 1.09 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, *J* = 3.1 Hz), 146.0 (d, *J* = 14.6 Hz), 119.6 (d, *J* = 10.7 Hz), 90.1, 74.4, 62.3 (d, *J* = 6.1 Hz), 60.3 (d, *J* = 3.1 Hz), 52.3, 24.8 (d, *J* = 140.3 Hz), 16.6 (d, *J* = 6.1 Hz), 13.8, 12.6; IR (neat) 2981, 1725, 1651, 1252, 1104, 1023, 962 cm^{-1}; LRMS m/z calcd for $C_{14}H_{24}O_6P$ 319.1 $[M+H]^+$, found 319.3.

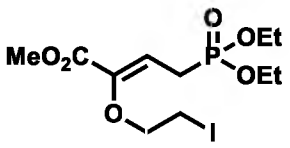


3.25

Methyl-*Z*-4-(diethoxyphosphoryl)-2-phenoxybut-2-enoate (3.25). Phenyl enol ether **3.25** was prepared according to the general procedure given for the formation of **3.17** using 25 mg (0.095 mmol) of **3.4**, 18 mg (0.19 mmol) phenol and 0.8 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 17.4 mg of **3.25** (56%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.25: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.3 Hz, 2H), 7.03 (dt, *J* = 7.3, 1.0 Hz, 1H), 6.91 (dd, *J* = 7.8, 0.9 Hz, 2H), 6.61 (dt, *J* = 7.9, 7.9 Hz, 1H), 4.09 (dq, *J*

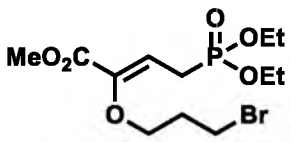
= 7.0, 7.0 Hz, 4H), 3.71 (s, 3H), 2.80 (dd, *J* = 22.5, 7.9 Hz, 2H), 1.30 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (d, *J* = 2.3 Hz), 157.1 (d, *J* = 2.3 Hz), 143.4, (d, *J* = 14.5 Hz), 129.8, 122.9, 121.2 (d, *J* = 9.9 Hz), 115.5, 62.4 (d, *J* = 6.2 Hz), 52.6, 24.8 (d, *J* = 140.4 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2983, 1734, 1661, 1491, 1256, 1214, 1024, 967 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_{22}O_6P$ 329.1 $[M+H]^+$, found 329.3.



3.26

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(2-iodoethoxy)but-2-enoate (3.26). 2-Iodoethyl enol ether **3.26** was prepared according to the general procedure given for the formation of **3.17** using 33 mg (0.13 mmol) of **3.4**, 20. µL (0.25 mmol) of 2-iodo-1-ethanol and 1 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 40. mg of **3.26** (78%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

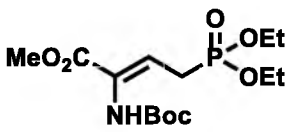
3.26: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 8.2, 6.7 Hz, 1H), 4.13 - 4.03 (m, 6H), 3.73 (s, 3H), 3.32 (t, *J* = 6.7 Hz, 2H), 2.84 (dd, *J* = 22.8, 8.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 146.5 (d, *J* = 14.1 Hz), 118.5 (d, *J* = 11.1 Hz), 72.6 (d, *J* = 3.1 Hz), 62.4 (d, *J* = 6.6 Hz), 52.4, 24.9 (d, *J* = 140.0 Hz), 16.6 (d, *J* = 6.0 Hz), 2.4; IR (neat) 2981, 1726, 1651, 1437, 1330, 1253, 1108, 1045, 1024, 964 cm^{-1}; LRMS *m/z* calcd for $C_{11}H_{21}IO_6P$ 407.0 $[M+H]^+$, found 407.0.



3.27

Methyl-*Z*-2-(3-bromopropoxy)-4-(diethoxyphosphoryl)but-2-enoate (3.27). 3-Bromopropyl enol ether **3.27** was prepared according to the general procedure given for the formation of **3.17** using 41 mg (0.16 mmol) of **3.4**, 28 μL (0.31 mmol) of 3-bromo-1-propanol and 0.7 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 43 mg of **3.27** (74%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.27: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (dt, *J* = 7.8, 7.8 Hz, 1H), 4.14 - 4.06 (m, 4H), 3.96 (t, *J* = 5.9 Hz, 2H), 3.77 (s, 3H), 3.57 (t, *J* = 6.3 Hz, 2H), 2.78 (dd, *J* = 23.0, 8.3 Hz, 2H), 2.22 (p, *J* = 6.4 Hz, 2H), 1.31 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6 (d, *J* = 3.0 Hz), 147.2 (d, *J* = 14.4 Hz), 117.8 (d, *J* = 10.7 Hz), 70.1 (d, *J* = 3.1 Hz), 62.4 (d, *J* = 6.1 Hz), 52.3, 33.2, 30.1, 24.6 (d, *J* = 141.2 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2981, 1726, 1651, 1438, 1253, 1112, 1023, 964 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{23}BrO_6P$ $[M+H]^+$ 373.0 and 375.0, found 373.1 and 375.0.

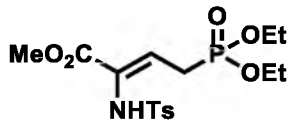


3.31

Methyl-*Z*-2-((tert-butoxycarbonyl)amino)-4-(diethoxyphosphoryl)but-2-enoate (3.31). *N*-Boc enamine **3.31** was prepared according to the general procedure given for the formation of **3.17** using 25 mg (0.095 mmol) of **3.4**, 22

mg (0.19 mmol) of *tert*-butyl carbamate and 0.8 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 26 mg of **3.31** (78%) as a colorless oil after flash chromatography (1:1 hexane/ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.31: ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (broad s, 1H), 6.33 (dt, *J* = 7.5, 7.5 Hz, 1H), 4.17-4.04 (m, 4H), 3.76 (s, 3H), 2.77 (dd, *J* = 22.5, 8.1 Hz, 2H), 1.43 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 153.3 (d, *J* = 1.6 Hz), 130.8, 121.9, 81.0, 62.6 (d, *J* = 6.9 Hz), 52.6, 28.3, 26.6 (d, *J* = 138.9 Hz), 16.6 (d, *J* = 5.4 Hz); IR (neat) 3231, 2980, 1721, 1656, 1497, 1367, 1247, 1164, 1046, 1025, 969 cm^{-1}; LRMS *m/z* calcd for $C_{14}H_{27}NO_7P$ 352.2 $[M+H]^+$, found 352.3.

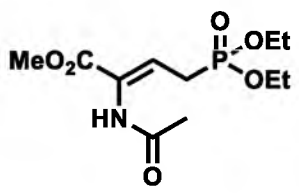


3.32

Methyl-*Z*-4-(diethoxyphosphoryl)-2-((4-methylphenyl)sulfonamido)but-2-enoate (3.32). *N*-Tosyl enamine **3.32** was prepared according to the general procedure given for the formation of **3.17** using 42 mg (0.16 mmol) of **3.4**, 41 mg (0.32 mmol) of toluenesulfonylamide and 0.7 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 32 mg of **3.32** (49%) as colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.32: ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.84 (dt, *J* = 8.1, 8.1 Hz, 1H), 6.68 (broad s, 1H), 4.18 - 4.06 (m, 4H), 3.50 (s, 3H), 3.06 (dd, *J* = 22.1, 7.8 Hz, 2H), 2.42 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1 (d, *J* = 2.3 Hz), 144.3, 136.5, 131.8 (d, *J* = 9.2 Hz), 129.7, 128.7 (d, *J* = 14.5 Hz), 127.8, 127.7 62.6 (d, *J* = 6.9 Hz), 52.7, 27.1

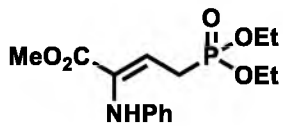
(d, *J* = 138.1 Hz), 21.8, 16.6 (d, *J* = 5.3 Hz); IR (neat) 2985, 1727, 1654, 1438, 1245, 1162, 1092, 1022, 969 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{25}O_7PS$ 406.1 $[M+H]^+$, found 406.1.



3.33

Methyl-*Z*-2-acetamido-4-(diethoxyphosphoryl)but-2-enoate (3.33). To a solution of diazo vinylphosphonate **3.4** (26 mg, 0.099 mmol) and acetamide (12 mg, 0.20 mmol) in toluene (2 mL) at rt was added $Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol). The reaction mixture was heated to 60 °C and stirred for 2h. After cooling to rt the reaction mixture was concentrated. Flash chromatography (30:1 CH_2Cl_2/MeOH) gave 16.6 mg of **3.33** (58%) as a colorless oil.

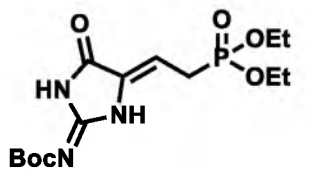
3.33: ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (br, 1H), 6.38 (dt, *J* = 8.1, 8.1 Hz, 1H), 4.12 - 4.02 (m, 4H), 3.74 (s, 3H), 2.69 (dd, *J* = 22.7, 7.9 Hz, 2H), 2.08 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 164.6 (d, *J* = 3.0 Hz), 131.2 (d, *J* = 13.1 Hz), 112.9 (d, *J* = 11.6 Hz), 62.8 (d, *J* = 7.1 Hz), 52.7, 26.6 (d, *J* = 139.0 Hz), 23.3, 16.6 (d, *J* = 6.1 Hz) IR (neat) 3250, 2986, 1729, 1693, 1517, 1438, 1370, 1246, 1024, 969 cm^{-1}; LRMS *m/z* calcd for $C_{11}H_{21}NO_6P$ $[M+H]^+$ 294.1, found 294.2



3.34

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(phenylamino)but-2-enoate (3.34). Phenyl enamine **3.34** was prepared according to the general procedure given for the formation of **3.17** using 25 mg (0.095 mmol) of **3.4**, 18 μL (0.19 mmol) of aniline and 0.8 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 22 mg of **3.34** (71%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

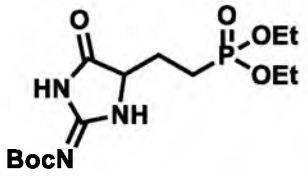
3.34: ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 - 7.15 (m, 2H), 6.85 - 6.80 (m 1H), 6.65 - 6.61 (m, 2H), 6.36-6.28 (m, 2H), 4.15 - 4.05 (m, 4H), 3.74 (s, 3H), 2.66 (dd, *J* = 22.8, 8.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.31 (dt, *J* = 7.1, 0.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0 (d, *J* = 2.3 Hz), 143.9, 133.6 (d, *J* = 12.9 Hz), 129.3, 120.2, 118.1 (d, *J* = 12.2 Hz), 115.8, 62.6 (d, *J* = 6.8 Hz), 52.6, 26.9 (d, *J* = 140.4 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 3291, 2984, 1731, 1639, 1602, 1491, 1438, 1245, 1024, 966 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_3NO_5P$ 328.1 $[M+H]^+$, found 328.1.



3.35

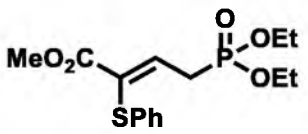
***tert*-butyl ((2E,4Z)-4-(2-(diethoxyphosphoryl)ethylidene)-5-oxoimidazolidin-2- ylidene)carbamate (3.35).** To a solution of **3.4** (69 mg, 0.26 mmol), N-Boc guanidine (84 mg, 0.53 mmol) and approximately 0.5 g 4Å molecular sieves in CH_2Cl_2 (3 mL) at rt was added $Rh_2(esp)_2$ (4.0 mg, 0.0053 mmol) in a single portion. The resulting yellow mixture was allowed to stir at rt for 1 day. Concentration and flash chromatography (1:5 hexanes:ethyl acetate then 1:20

MeOH:CH_2Cl_2 with 0.1% ammonium hydroxide) provided 55 mg of cyclic guanidine **3.35** (57%) as a colorless oil. Guanidine **3.35** was characterized as its hydrogenated derivative **3.36**.



3.36

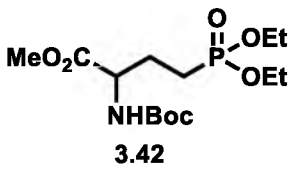
***tert*-Butyl 4-(2-(diethoxyphosphoryl)ethyl)-5-oxoimidazolidin-2-ylidenecarbamate (3.36).** To a solution of **3.36** (54 mg, 0.15 mmol) in ethyl acetate was added 10% Pd/C (32 mg, 0.030 mmol) at rt. The resulting mixture was allowed to react at rt under 1 atm H_2 atmosphere for 6 h. Filtrate through celite and concentrate. Flash chromatograpgy (1:20 MeOH:CH_2Cl_2 with 0.1% ammonium hydroxide) provided 46 mg of guanidine **3.36** (85%) as a colorless oil. **3.36**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (broad s, 1H), 4.17 - 4.05 (m, 5H), 2.29 - 2.19 (m, 1H), 2.05 - 1.88 (m, 2H), 1.85 - 1.74 (m, 1H), 1.53 (s, 9H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.31 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.7, 167.3, 155.2, 83.2, 62.1 (d, *J* = 6.9 Hz), 59.8, 28.2 (d, *J* = 2.3 Hz), 25.3, 22.0 (d, *J* = 141.5 Hz), 16.7 (d, *J* = 3.2 Hz), 16.6 (d, *J* = 2.2 Hz); IR (neat) 2924, 1735, 1671, 1621, 1592, 1561, 1243, 1148, 1022, 959 cm^{-1}; LRMS m/z calcd for $C_{14}H_{27}N_3O_6P$ $[M+H]^+$ 364.2, found 364.3.



3.38

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(phenylthio)but-2-enoate (3.38). Thiophenyl ether **3.38** was prepared according to the general procedure given for the formation of **3.17** using 33 mg (0.13 mmol) of **3.4**, 26 µL (0.25 mmol) of thiophenol and 0.9 mg (0.002 mmol) of $Rh_2(OAc)_4$ to give 35.1 mg of **3.38** (81%) as a colorless oil after flash chromatography (1:1 hexane/ ethyl acetate, SiO_2 was neutralized with 1% NEt_3).

3.38: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (dt, *J* = 7.8, 6.9 Hz, 1H), 7.26 - 7.21 (m, 4H), 7.18 - 7.15 (m, 1H), 4.15 - 4.09 (m, 4H), 3.64 (s, 3H), 3.18 (dd, *J* = 23.5, 8.4 Hz, 2H), 1.32 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (d, *J* = 3.1 Hz), 141.6 (d, *J* = 11.4 Hz), 135.0 (d, *J* = 2.3 Hz), 130.8 (d, *J* = 14.5 Hz), 129.2, 128.8, 126.7, 62.6 (d, *J* = 6.9 Hz), 52.9 (d, *J* = 2.3 Hz), 30.1 (d, *J* = 138.1 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 2983, 1718, 1653, 1437, 1250, 1023, 966 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_{22}O_5PS$ 345.1 $[M+H]^+$, found 345.3.

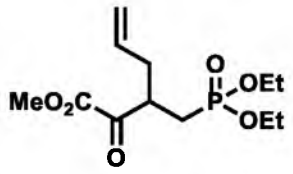


3.42

Methyl 2-((*tert*-butoxycarbonyl)amino)-4-(diethoxyphosphoryl)butanoate (3.42). To a solution of N-Boc enamine **3.31** (25 mg, 0.071 mmol) in ethyl acetate (3 mL) at rt was added Pd/C (10%, 8.0 mg (0.0075 mmol)). The resulting mixture was subjected to H_2 (1 atm). After 12 h the reaction mixture was filtered through celite. Concentration and flash chromatography (1:5 hexanes/ethyl acetate) gave 25 mg of **3.42** (98%) as a colorless oil.

3.42: ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (broad d, *J* = 8.1 Hz, 1H), 4.26 - 4.16 (m, 1H), 4.03 - 3.91 (m, 4H), 3.63 (s, 3H), 2.15 - 1.94 (m, 2H), 1.88 - 1.59 (m, 2H),

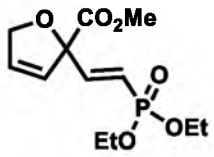
1.32 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 155.6, 80.3, 61.9 (d, *J* = 6.7 Hz), 53.7 (d, *J* = 17.7 Hz), 52.7, 28.5, 26.2 (d, *J* = 3.7 Hz), 22.0 (d, *J* = 143.4 Hz), 16.6 (d, *J* = 6.1 Hz); IR (neat) 3266, 2979, 1745, 1710, 1526, 1447, 1392, 1366, 1244, 1216, 1164, 1051, 1024, 963 cm^{-1}; LRMS m/z calcd for $C_{14}H_{29}NO_7P$ $[M+H]^+$ 354.2, found 354.3.



3.56

Methyl 3-((diethoxyphosphoryl) methyl)-2-oxohex-5-enoate (3.56). A solution of **3.19** (58 mg, 0.20 mmol) in toluene was stirred at 80 °C for 16 h, cooled to rt and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) provided 43 mg of ketoester **3.56** (74%) as a colorless oil.

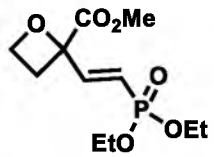
3.56: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (ddt, *J* = 17.1, 9.8, 7.3 Hz, 1H), 5.07 (d, *J* = 9.7 Hz, 1H), 5.05 (d, *J* = 18.1 Hz, 1H), 4.09 - 3.97 (m, 4H), 3.85 (s, 3H), 3.76 - 3.68 (m, 1H), 2.47 (ddd, *J* = 14.2, 6.3, 6.3 Hz, 1H), 2.31 - 2.18 (m, 2H), 1.91 (ddd, *J* = 18.4, 15.6, 3.9 Hz, 1H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.25 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8 (d, *J* = 5.5 Hz), 161.1, 133.4, 119.1, 62.1 (d, *J* = 6.7 Hz), 61.9 (d, *J* = 6.1 Hz), 53.2, 41.4 (d, *J* = 3.7 Hz), 36.7 (d, *J* = 13.4 Hz), 26.2 (d, *J* = 142.2 Hz), 16.5 (d, *J* = 5.5 Hz), 16.4 (d, *J* = 6.1 Hz); IR (neat) 2982, 1729, 1641, 1441, 1240, 1020, 959, 804 cm^{-1}; LRMS m/z calcd for $C_{12}H_{22}O_6P$ $[M+H]^+$ 293.2, found 293.2.



3.61

Methyl-*E*-2-(2-(diethoxyphosphoryl)vinyl)-2,5-dihydrofuran-2-carboxylate (3.61). To a solution of enol ether **3.21** (41.7 mg, 0.140 mmol) in acetone (2 mL) in the dark was added $AgNO_3$ (4.9 mg, 0.0029 mmol) and DBU (26 µL, 0.17 mmol). The resulting reaction mixture was allowed to stir at rt for 3 h and was then concentrated. Flash chromatography (1:5 hexanes/ethyl acetate) gave 37.7 mg of **3.61** (90%) as colorless oil.

3.61: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (dd, *J* = 22.0, 17.1 Hz, 1H), 6.10 (dd, *J* = 20.0, 17.1 Hz, 1H), 6.00 (d, *J* = 5.9 Hz, 1H), 5.87 (dt, *J* = 6.4, 2.4 Hz, 1H), 4.89 (dt, *J* = 13.7, 1.5 Hz, 1H), 4.78 (dt, *J* = 13.7, 1.4 Hz, 1H), 4.10 - 4.00 (m, 4H), 3.74 (s, 3H), 1.29 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 148.4 (d, *J* = 6.9 Hz), 128.9, 127.4 (d, *J* = 2.3 Hz), 117.4 (d, *J* = 187.7 Hz), 93.1 (d, *J* = 20.6 Hz), 76.9, 62.2 (d, *J* = 5.4 Hz), 62.1 (d, *J* = 5.3 Hz), 53.1, 16.6 (d, *J* = 6.1 Hz) ; IR (neat) 2983, 2955, 2866, 1756, 1733, 1632, 1437, 1392, 1251, 1024, 964 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{20}O_6P$ 291.1 $[M+H]^+$, found 291.2.

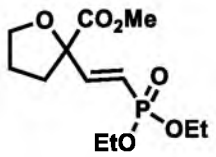


3.74

Methyl-*E*-2-(2-(diethoxyphosphoryl)vinyl)oxetane-2-carboxylate (3.74). To a solution of iodide **3.26** (30. mg, 0.074 mmol) in acetone (3 mL) at rt was added DBU (13 µL, 0.089 mmol) dropwise. After stirring at rt overnight, the reaction

mixture was concentrated. Flash chromatography (1:5 hexane/ethyl acetate) gave 12 mg of oxetane **3.74** (56%) as a colorless oil.

3.74: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 21.7, 16.9 Hz, 1H), 6.28 (dd, *J* = 19.6, 16.9 Hz, 1H), 4.62 - 4.69 (m, 1H), 4.54 - 4.47 (m, 1H), 4.16 - 4.03 (m, 4H), 3.80 (s, 3H), 3.06 - 2.96 (m, 1H), 2.77 - 2.68 (m, 1H), 1.34 (t, *J* = 7.3 Hz, 3H), 1.31 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 148.8 (d, *J* = 6.9 Hz), 118.0 (d, *J* = 188.5 Hz), 85.5 (d, *J* = 21.4 Hz), 66.4, 62.3 (d, *J* = 5.3 Hz), 62.2 (d, *J* = 5.3 Hz), 53.1, 32.8 (d, *J* = 2.3 Hz), 16.6 (d, *J* = 6.1 Hz), 16.6 (d, *J* = 5.3 Hz); IR (neat) 2981, 2917, 1756, 1735, 1634, 1438, 1393, 1250, 1107, 1025, 963 cm^{-1}; LRMS *m/z* calcd for $C_{11}H_{20}O_6P$ 279.1 $[M+H]^+$, found 279.1.

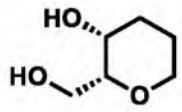


3.76

Methyl-*E*-2-(2-(diethoxyphosphoryl)vinyl)tetrahydrofuran-2-carboxylate (3.76). To a solution of bromide **3.27** (24 mg, 0.064 mmol) in acetone (3 mL) at rt was added DBU (12 µL, 0.076 mmol) dropwise. After 4 h the resulting reaction mixture was concentrated. Flash chromatography (1:5 hexane/ethyl acetate) gave 17 mg of **3.76** (91%) as a colorless oil.

3.76: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 21.4, 16.6 Hz, 1H), 6.06 (dd, *J* = 20.0, 17.1 Hz, 1H), 4.10 - 4.01 (m, 6H), 3.74 (s, 3H), 2.36 (ddd, *J* = 12.7, 7.3, 7.3 Hz, 1H), 2.05-1.86 (m, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.29 (t. *J* = 7.4 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 150.4 (d, *J* = 6.9 Hz), 116.8 (d, *J* = 187.7 Hz), 86.1 (d, *J* = 19.9 Hz), 70.2, 62.2 (d, *J* = 5.4 Hz), 62.1 (d, *J* = 5.3 Hz), 53.0, 36.9

(d, *J* = 2.3 Hz), 25.1, 16.6 (d, *J* = 6.1 Hz), 16.5 (d, *J* = 4.6 Hz); IR (neat) 2982, 1752, 1732, 1631, 1442, 1392, 1247, 1201, 1093, 1019, 959 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{22}O_6P$ 293.1 $[M+H]^+$, found 293.2.

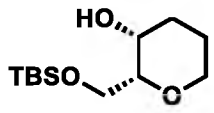


3.110

(2*R*,3*R*)-2-(Hydroxymethyl)tetrahydro-*2H*-pyran-3-ol (**3.110)**. To a solution of **3.109** (0.189 g, 0.882 mol) in ethyl acetate at rt was added 10% Pd/C (47 mg, 0.044 mmol). The resulting mixture was stirred under H_2 (1 atm) for 6 h. The reaction mixture was then filtered through a pack of celite and concentrated. The crude product was used for the next step without further purification.

The crude mixture from above was dissolved in a 9:6:1 mixture of MeOH/H_2O/Et_3N (8 mL) and stirred for 3h at rt. Concentrate and flash chromatography (1: 5 hexane/ethyl acetate) provided 0.106 g of diol **3.110** (91%) as a colorless oil.

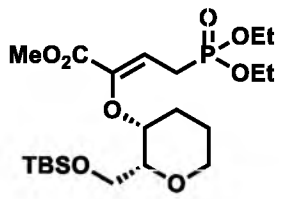
3.110: $[\alpha]_D^{20}$ = 5.7 (c = 0.85, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 3.98 - 3.96 (m, 1H), 3.81 (broad s, 1H), 3.75 - 3.70 (m, 2H), 3.57 (broad s, 2H), 3.48 - 3.42 (m, 1H), 3.34 - 3.32 (m, 1H), 2.88 (broad s, 1H), 2.00 - 1.86 (m, 2H), 1.64 - 1.56 (m, 1H), 1.34 (broad d, *J* = 13.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.4, 68.7, 66.3, 64.0, 30.5, 20.3; IR (neat) 3358 (broad), 2939, 2850, 1650, 1438, 1274, 1211, 1090, 1055, 1029, 1001, 964 cm^{-1}; LRMS *m/z* calcd for $C_6H_{13}O_{3Na}$ $[M+Na]^+$ 155.1, found 155.1.



3.107

(2*R*,3*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-ol (3.107). To a solution of diol **3.110** (0.280 g, 2.12 mmol) and imidazole (0.217 g, 3.18 mmol) in DMF (5 mL) at 0 °C was added TBSCl (0.352 g, 2.33 mmol). The resulting reaction mixture was warmed to rt and stirred for an additional 2 h. The reaction was quenched with $NaHCO_3$ (aq, 5 mL) and then the resulting mixture was diluted with H_2O (15 mL). The mixture was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified using flash chromatography (3:1 hexanes/ethyl acetate) to give 0.481g of **3.107** (92%) as a colorless oil.

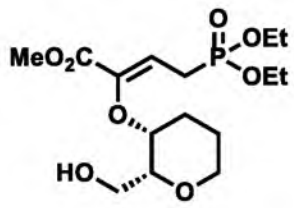
3.107: $[\alpha]_D^{20}$ = -11.5 (c = 1.58, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 - 3.96 (m, 1H), 3.88 (broad s, 1H), 3.78 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.74 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.45 (ddd, *J* = 13.7, 11.8, 2.5 Hz, 1H), 3.30 (ddd, *J* = 5.4, 5.4, 1.0 Hz, 1H), 2.91 (d, *J* = 5.5 Hz, 1H), 2.03 - 1.90 (m, 2H), 1.63 - 1.56 (m, 1H), 1.36 - 1.32 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.3, 68.8, 65.9, 64.7, 30.5, 26.1, 20.4, 18.5, -5.2, -5.3; IR (neat) 3446 (broad), 2928, 2855, 1472, 1463, 1252, 1097 cm^{-1}; LRMS *m/z* calcd for $C_{12}H_{27}O_3Si$ $[M+H]^+$ 247.2, found 247.3.



3.111

Methyl-*Z*-2-(((2*R*,3*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-pyran-3-yl)oxy)-4-(diethoxyphosphoryl)but-2-enoate (3.111). To a solution of diazo vinyl phosphonate **3.4** (0.100 g, 0.38 mmol) and alcohol **3.107** (63 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) at rt was added $Rh_2(OAc)_4$ (1 mg, 0.002 mmol). The reaction mixture was concentrated after 10 h. Flash chromatography (1:1 hexanes/ethyl acetate, SiO_2 was neutralized with 1% NEt_3) gave 83 mg of **3.111** (68%) as a colorless oil.

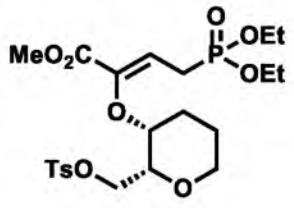
3.111: $[\alpha]_D^{20}$ = -18.3 (c = 1.26, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 7.9, 7.9 Hz, 1H), 4.42 (br, 1H), 4.14 - 4.05 (m, 4H), 4.02 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.80 (dd, *J* = 10.2, 5.9 Hz, 1H), 3.73 (s, 3H), 3.72 (partially obscured dd, *J* = 11.2, 6.3 Hz, 1H), 3.48-3.42 (m, 2H), 2.96-2.82 (m, 2H), 1.97 - 1.85 (m, 2H), 1.58 - 1.51 (m, 1H), 1.37 - 1.27 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 6H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 145.8 (d, *J* = 14.7 Hz), 116.0 (d, *J* = 11.0 Hz), 80.5, 72.6, 68.2, 63.4, 62.3 (d, *J* = 5.5 Hz), 62.2 (d, *J* = 6.1 Hz), 52.1, 27.5, 26.1, 24.5 (d, *J* = 141.4 Hz), 21.2, 18.6, 16.6 (d, *J* = 6.1 Hz), -5.1, -5.2; IR (neat) 2954, 2929, 2854, 1728, 1647, 1437, 1340, 1253, 1101, 1049, 1027, 965 cm^{-1}; LRMS *m/z* calcd for $C_{21}H_{42}O_8PSi$ $[M+H]^+$, 481.2, found 481.3



3.112

Methyl-*Z*-4-(diethoxyphosphoryl)-2-(((2*R*,3*R*)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)oxy)but-2-enoate (3.112). To a solution of **3.111** (221 mg, 0.460 mmol) in ethanol (10 mL) at rt was added PPTS (127 mg, 0.506 mmol). After stirring for 8 h, the reaction mixture was concentrated. Flash chromatography (30:1 CH_2Cl_2/MeOH) gave 124 mg of **3.112** (74%) as a colorless oil.

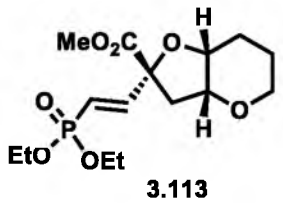
3.112: $[\alpha]_D^{20}$ = -35.4 (c = 0.68, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dt, *J* = 7.8, 7.8 Hz, 1H), 4.08 (br, 1H), 4.05 - 3.97 (m, 4H), 3.94 - 3.91 (m, 1H), 3.74 (dd, *J* = 11.2, 7.8 Hz, 1H), 3.67 (s, 3H), 3.56 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.44 - 3.37 (m, 2H), 2.82-2.70 (m, 2H), 1.92 - 1.84 (m, 2H), 1.49 - 1.42 (m, 1H), 1.37 - 1.33 (m, 1H), 1.21 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (d, *J* = 2.5 Hz), 145.2 (d, *J* = 14.0 Hz), 119.1 (d, *J* = 9.8 Hz), 79.0, 72.8 (d, *J* = 1.8 Hz), 68.1, 62.3 (d, *J* = 3.7 Hz), 62.3 (d, *J* = 3.1 Hz), 61.5, 52.7, 26.4, 24.8 (d, *J* = 141.6 Hz), 21.4, 16.5 (d, *J* = 6.1 Hz); IR (neat) 3419 (broad), 2953, 2850, 1723, 1646, 1438, 1278, 1246, 1093, 1017, 960 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_{28}O_8P$ $[M+H]^+$ 367.1, found 367.2.



3.106

Methyl- *Z*-4- (diethoxyphosphoryl)-2- (((2*R*,3*R*)-2- ((tosyloxy) methyl) tetrahydro- *2H*-pyran-3-yl)oxy)but-2-enoate (3.106). To a solution of **3.112** (140. mg, 0.382 mmol) NEt_3 (80. µL, 0.57 mmol), and DMAP (5.0 mg, 0.038 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TsCl (80 mg, 0.42 mmol). The reaction mixture was allowed to warm to rt and stirred for an additional 6 h. Concentration and flash chromatography (1:5 hexanes/ethyl acetate) gave 178 mg of **3.106 (**89%) as a colorless oil.

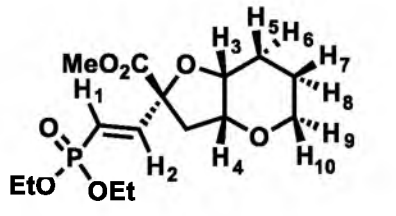
3.106: $[\alpha]_D^{20}$ = -6.9 (c = 1.17, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 6.18 (dt, *J* = 7.8, 7.8 Hz, 1H), 4.42 (dd, *J* = 11.2, 3.4 Hz, 1H), 4.25 (broad d, *J* = 1.5 Hz, 1H), 4.15 (dd, *J* = 11.3, 8.3 Hz, 1H), 4.10 - 4.03 (m, 4H), 3.97 - 3.95 (m, 1H), 3.73 (s, 3H), 3.68 (ddd, *J* = 7.8, 3.4, 2.0 Hz, 1H), 3.39 (ddd, *J* = 12.2, 12.2, 2.0 Hz, 1H), 2.84-2.71 (m, 2H), 2.41 (s, 3H), 1.90 - 1.80 (m, 2H), 1.54 - 1.47 (m, 1H), 1.38 - 1.35 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 (d, *J* = 2.3 Hz), 145.0 (d, *J* = 14.5 Hz), 144.9, 133.3, 130.0, 128.2, 117.8 (d, *J* = 10.7 Hz), 77.0, 72.9 (d, *J* = 2.3 Hz), 71.0, 67.9, 62.4 (d, *J* = 3.1 Hz), 62.3 (d, *J* = 3.8 Hz), 52.3, 26.6, 24.6 (d, *J* = 141.2 Hz), 21.8, 20.9, 16.6 (d, *J* = 6.1 Hz); IR (neat) 2957, 2851, 1724, 1653, 1362, 1253, 1177, 1096, 1048, 1025, 960 cm^{-1}; LRMS *m/z* calcd for $C_{22}H_{34}O_{10}PS$ $[M+H]^+$ 521.2, found 521.3.



3.113

Methyl (2*R*,3a*R*,7a*R*)-2-((*E*)-2-(diethoxyphosphoryl)vinyl)hexahydro-2H-furo[*3,2-b*]pyran-2-carboxylate (3.113). To a solution of tosylate **3.106** (150 mg, 0.286 mmol) and acetone (5 mL) at rt was added DBU (52 µL, 0.35 mmol) dropwise. After stirring for 12 h, the reaction mixture was concentrated. Flash chromatography (1:5 hexane/ethyl acetate) gave 85 mg of **3.113** (85%) as a colorless oil.

3.113: $[\alpha]_D^{20}$ = 48.6 (c = 2.49, $CHCl_3$) ^{1}H NMR (500 MHz, C_6D_6) δ 7.30 (dd, *J* = 21.5, 16.6 Hz, 1H), 6.42 (dd, *J* = 19.6, 17.1 Hz, 1H), 3.98 - 3.85 (m, 4H), 3.78 - 3.77 (m, 1H), 3.49 - 3.46 (m, 1H), 3.38 (dd, *J* = 4.4, 2.0 Hz, 1H), 3.20 (s, 3H), 2.81 (ddd, *J* = 12.7, 12.7, 1.5 Hz, 1H), 2.17 (dd, *J* = 14.1, 4.9 Hz, 1H), 2.05 (d, *J* = 13.7 Hz, 1H), 1.92 (ddd, *J* = 14.7, 4.4, 2.0 Hz, 1H), 1.64 (ddddd, *J* = 26.3, 12.7, 3.9, 3.9 Hz, 1H), 1.22-1.15 (m, 1H), 1.01 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.82 - 0.77 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.6 (d, *J* = 1.5 Hz), 151.4 (d, *J* = 7.6 Hz), 117.4 (d, *J* = 187.2 Hz), 84.6 (d, *J* = 20.6 Hz), 77.9, 76.3, 66.1, 61.4 (d, *J* = 5.3 Hz), 61.3 (d, *J* = 6.1 Hz), 51.9, 44.7 (d, *J* = 2.3 Hz), 24.9, 20.4, 16.3 (d, *J* = 5.3 Hz); IR (neat) 2925, 2852, 1733, 1635, 1437, 1243, 1104, 1054, 1022, 964 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_{26}O_7P$ $[M+H]^+$ 349.1, found 349.2.



Summary of 1D NOE data for compound **3.113** (400 Hz, C_6D_6):

Irradiation at 1.64 ppm (H-8) resulted in enhancement at 6.42 ppm (H-2);

Irradiation at 6.42 ppm (H-2) resulted in enhancement at 1.64 ppm (H-8);

3.7 References

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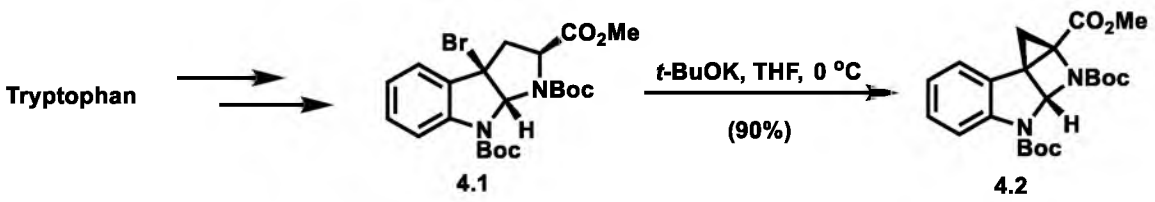
CHAPTER 4

VINYL DIAZO PHOSPHONATES AS PRECURSORS FOR FURANS

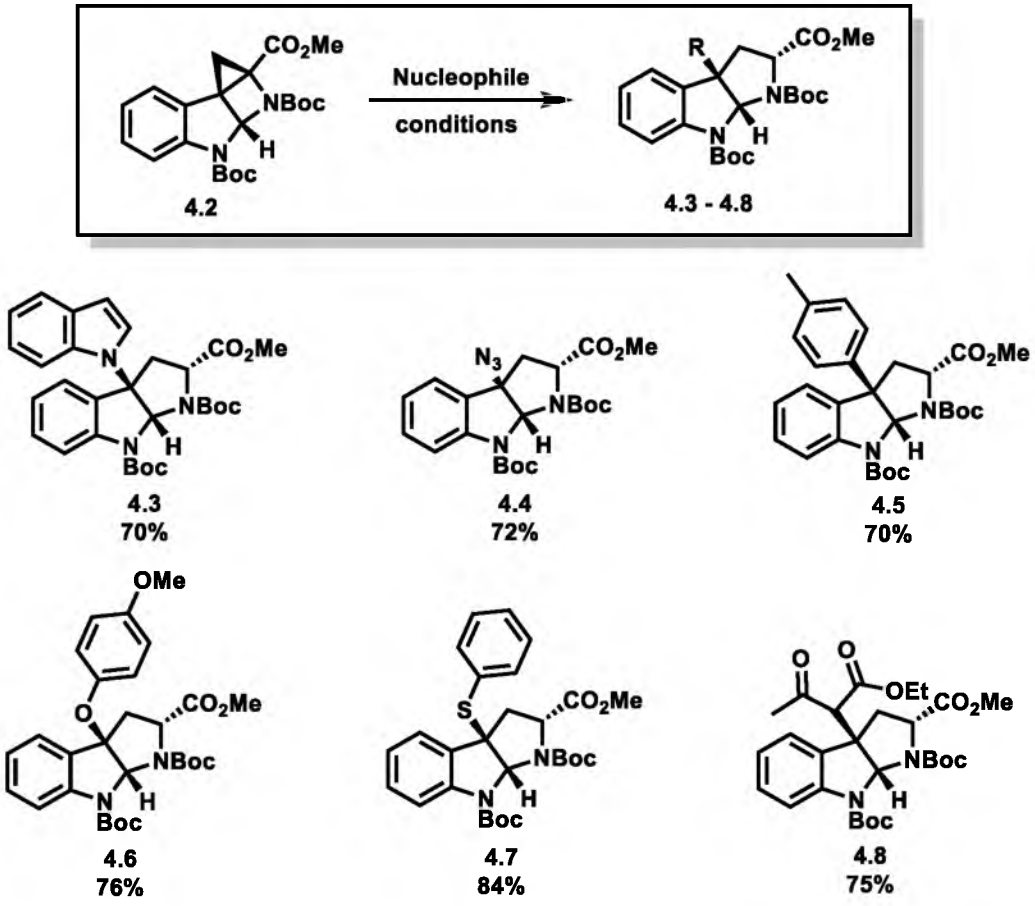
4.1 Synthesis of furans bearing a pyrollylindoline scaffold

In 2010, former group member Dr. Espejo discovered that when treating 3-bromoindoline **4.1** with base, cyclopropylazetoindoline **4.2** was formed (Scheme 4.1).[1] This highly strained compound could serve as an efficient and versatile electrophile to react with carbon or heteroatom based nucleophiles (Scheme 4.2).

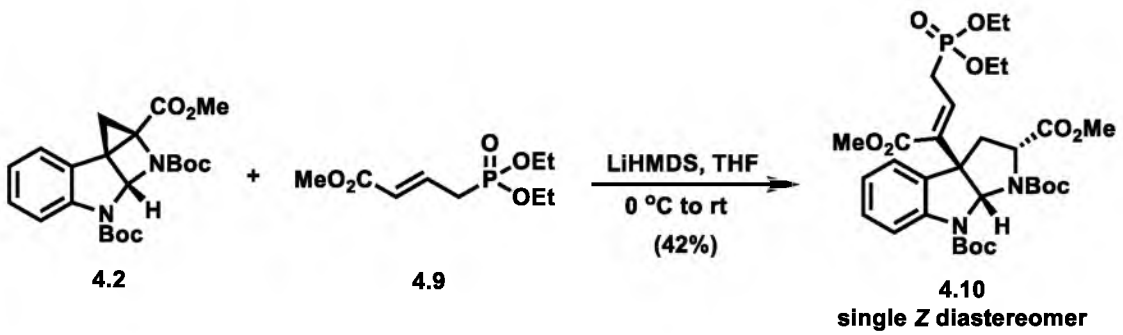
In Chapter 2, we demonstrated that chemo- and stereoselective alkylation of phosphonocrotonate **4.9** was viable.[2] We envisioned that it would be worthwhile to see whether the alkylation of **4.9** with the highly electrophilic cyclopropylazetoindoline **4.2** would be possible. To test that, a solution of **4.2** was added into a premixed THF solution of phosphonocrotonate **4.9** and LiHMDS. To our delight, a single product **3.28** was obtained and ^{1}H NMR suggested it was the desired mono-alkylation product (Scheme 4.3). The unusual chemical shift of the vinyl proton drew our attention. Compared to the other alkylated products from **4.9**, the chemical shift of the vinyl proton moved significantly more upfield (5.5 ppm vs ~6.7 ppm). We suspected that this was due to the bulky pyrroloindoline substitution forcing **3.28** to adopt the *Z* geometry. The NOE experiments confirmed our assumption.



Scheme 4.1 Synthesis of cyclopropylazetoindoline

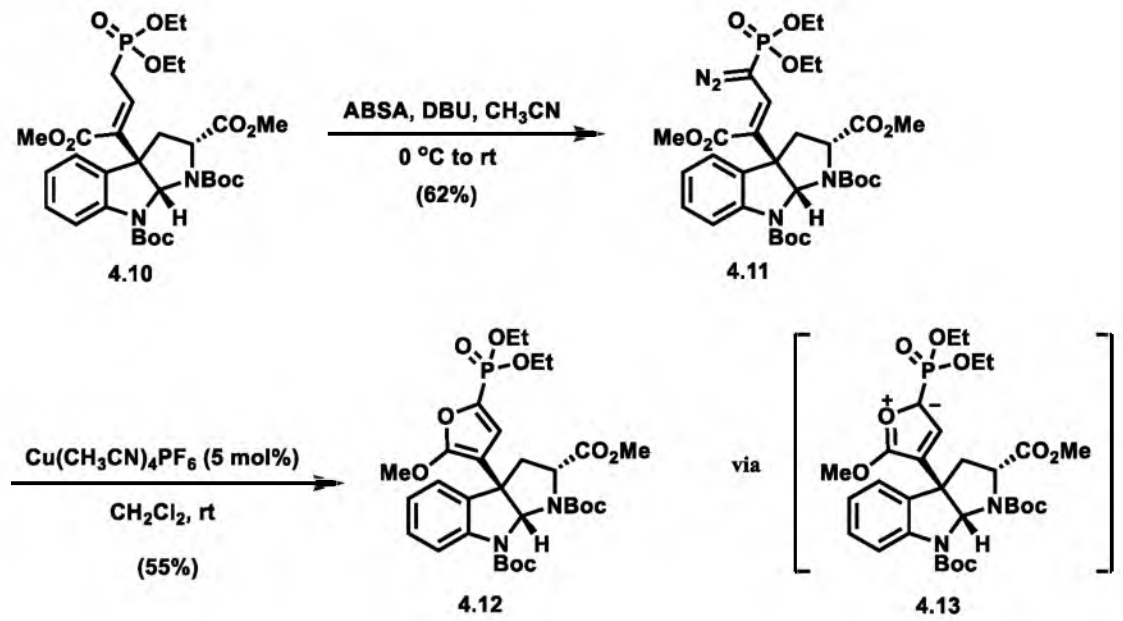


Scheme 4.2 Reaction of cyclopropylazetoindoline with nucleophiles



Scheme 4.3 Alkylation of phosphonate with cyclopropylazetoindoline

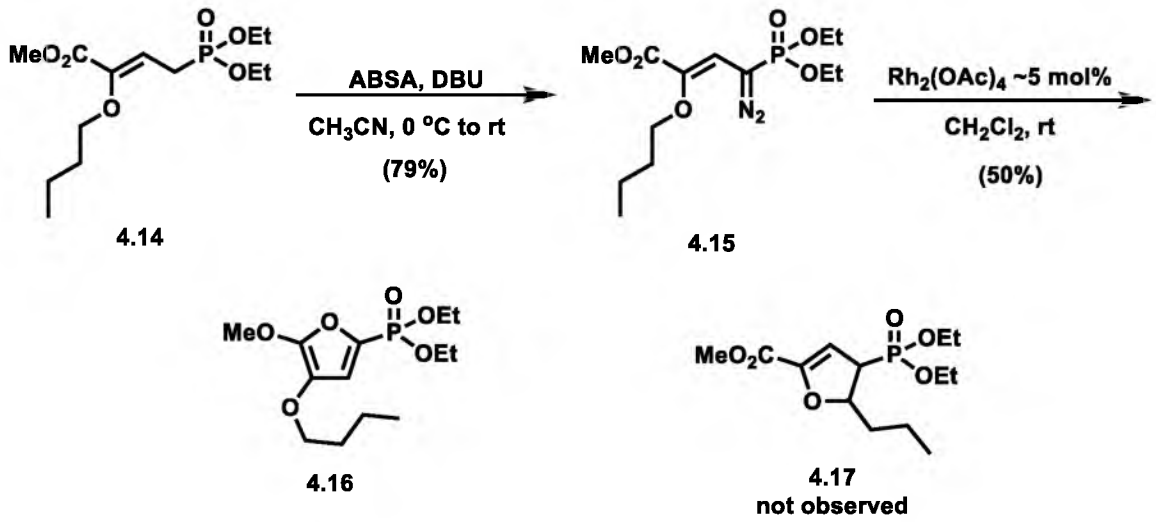
Under standard diazo transfer conditions **4.10** provided diazo **4.11** smoothly (Scheme 4.4). Furan **4.12** was obtained when **4.11** was treated with $Cu(CH_3CN)_4PF_6$. We believe that the *Z*-geometry is necessary for the furan formation through the cyclic oxonium ylide intermediate **4.13**. Note that in Chapter 2, we showed that *E*-vinyl diazo phosphonates exclusively gave cyclopentenes when treating with $Rh_2(OAc)_4$.



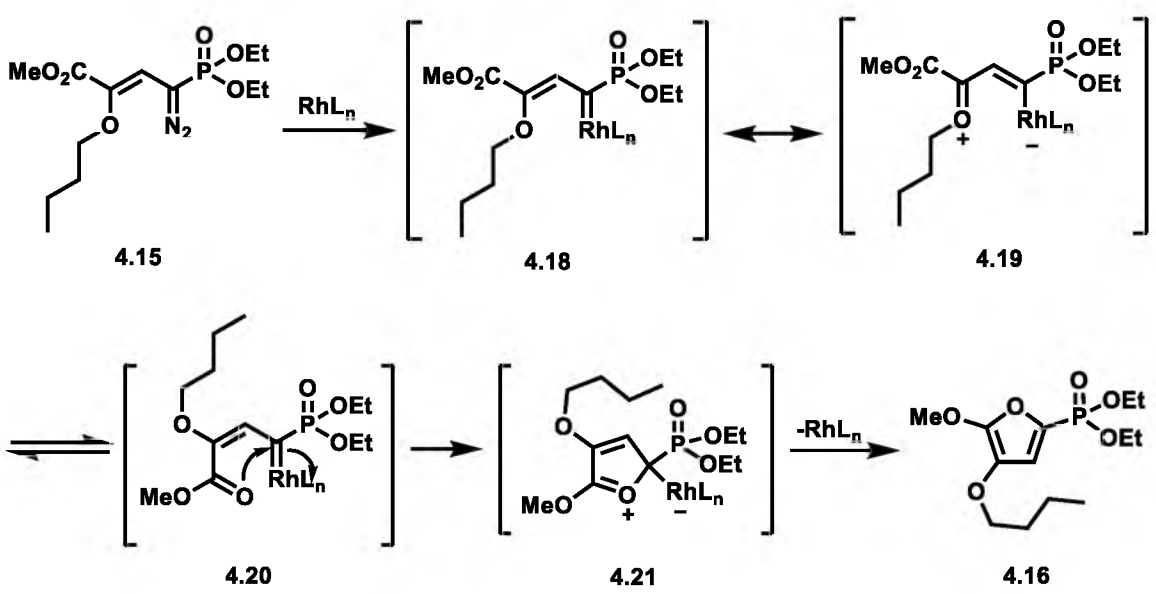
Scheme 4.4 Synthesis of furan from *Z*-vinyl diazo phosphonate

4.2 Synthesis of furans via an *E/Z* isomerization

We were very excited about the formation of furan **4.12** because furan phosphonic acid had been shown to be useful pharmaceuticals.[3] In our exploration for the synthetic applications of the X-H insertion products, we discovered that a second diazo transfer reaction on the O-H insertion product such as **4.14** was feasible (Scheme 4.5). When treating diazo **4.15** with $Rh_2(OAc)_4$ a single product was obtained. To our surprise, the NMR data indicated that neither dihydrofuran **4.17** nor the carbene dimer was formed; instead, furan **4.16** was obtained. Since NOE experiment clearly showed that in the diazo precursor **4.15** the ester group was *trans* to the diazo functionality, the only possible mechanism for the formation of furan **4.16** was by an *E/Z* alkene isomerization (Scheme 4.6). We believe that the enol ether present in **4.15** facilitated the isomerization.



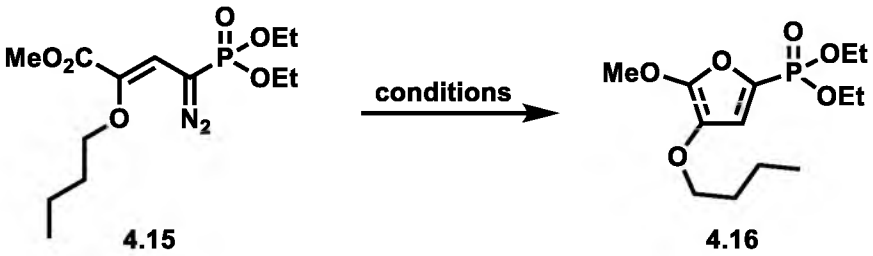
Scheme 4.5 Formation of furan from *Z*- diazo phosphonate



Scheme 4.6 Proposed mechanism of furan formation

The reaction conditions were further optimized as shown in Table 4.1. The catalyst played an important role in this reaction. $Rh_2(OAc)_4$ was largely deactivated possibly because of substrate binding, and a significant amount of starting material (35%) was recovered. Treating diazo **4.15** with copper catalyst led to mostly decomposition. More robust catalysts such as $Rh_2(esp)_2$ and $Rh_2(Oct)_4$ gave much better results in terms of yield. The optimal conditions were determined to be slowly injection of the diazo compound via a syringe pump into a solution of $Rh_2(Oct)_4$ catalyst, and the yield of **4.16** was improved to 70% when the optimized conditions were applied. Reactions in hexane provided minimal amount of product. Thermal conditions failed to provide any desired product either, suggesting that the metal carbenoid formation was necessary for the key isomerization to happen. To the best of our knowledge, this is the first example that furans were synthesized via the *E*/*Z* isomerization of vinyl carbenoids.

Table 4.1 Optimization of furan formation



4.15 **4.16**

entry	catalyst(eq)	solvent	temp.	yield
1	$Rh_2(OAc)_4$ (0.02)	CH_2Cl_2	rt	20%
2	$Cu(CH_3CN)PF_6$ (0.02)	CH_2Cl_2	rt	15%
3	$Rh_2(esp)_2$ (0.02)	CH_2Cl_2	rt	45%
4	none	toluene	80°C	no rxn.
5	$Rh_2(OAc)_4$ (0.02)	hexane	rt	no rxn.
6	$Rh_2(CF_3CO_2)_4$ (0.02)	CH_2Cl_2	rt	trace
7	$Rh_2(Oct)_4$ (0.02)	CH_2Cl_2	rt	45%
8	$Rh_2(Oct)_4$ (0.02)	hexane	rt	trace
9	$Rh_2(Oct)_4$ (0.02)[a]	CH_2Cl_2	rt	62%
10	$Rh_2(Oct)_4$ (0.02)[b]	CH_2Cl_2	rt	70%

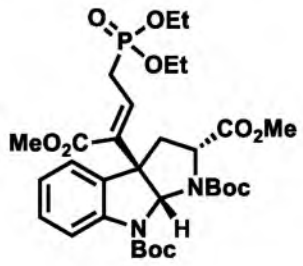
[a] injected with syringe pump in 0.5h
[b] injected with syringe pump in 2h

4.3 Conclusion

Furan **4.12** bearing a pyrroloindoline scaffold was successfully synthesized from a *Z*-vinyl diazo phosphonate **4.11.** An *E*/*Z* isomerization occurred when treating diazo **4.15** with a rhodium catalyst and furan **4.16** was formed, which has never been documented in literature. Currently, we are exploring the substrate scope of this isomerization/cyclization cascade to generate more furan phosphonates.

4.4 Experimental

NMR spectra were recorded on a Varian Unity-300, Varian Inova-400 or a Varian VXR-500 spectrometers. Chemical shifts were reported in δ, parts per million (ppm), relative to chloroform (7.25) or dichloromethane (5.29) as internal standards. Coupling constants, J, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Solvents were purified according to the guidelines in Purification of Common Laboratory Chemicals (Armarego. W. L. F. and Chai, C. L. L., Oxford, 2009). Spectroscopic grade CH_3CN was stored over activated 4Å molecular sieves and used without additional purification. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of dried nitrogen in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

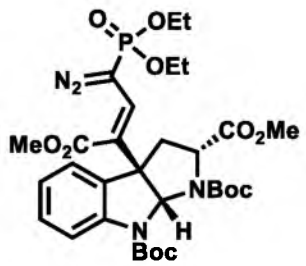


4.10

(2R,3aS,8aR)-1,8-di-tert-butyl 2-methyl 3a-((*Z*)-4-(diethoxyphosphoryl)-1-methoxy-1-oxobut-2-en-2-yl)-3,3a-dihydropyrrolo[2,3-b]indole-1,2,8(2H,8aH)

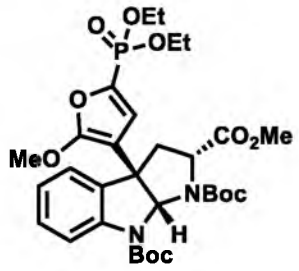
-tricarboxylate (4.10). To a solution of phosphonocrotonate **4.9** (91 mg, 0.39 mmol) in THF (5 mL) was added LiHMDS (0.40 mL, 1M solution in THF, 0.40 mmol) dropwise at 0 °C. After stir for 15 min at 0 °C, a solution of cyclopropylazetoindoline **4.2** (0.241 g, 0.579 mmol) in THF (2 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 2h at rt and quenched with sat. NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (1:2 hexane/ethyl acetate) provided 0.168 g of phosphonate **4.10** (46%) as a colorless oil.

4.10: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (br, 1H), 7.23 - 7.18 (m, 1H), 7.03 - 6.94 (m, 2H), 6.43 (s, 1H), 5.62 (dt, *J* = 7.8, 7.8 Hz, 1H), 4.61 (br, 1H), 4.04 - 3.93 (m, 4H), 3.74 (m, 3H), 3.11 (s, 3H), 3.86 (dd, J = 12.7, 8.1 Hz, 2H), 2.68 - 2.66 (m, 2H), 1.55 (s, 9H), 1.44 (br, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.2 (d, *J* = 3.5 Hz), 152.4, 143.5, 137.1 (d, *J* = 14.1 Hz), 132.3, 129.9 (d, *J* = 10.6 Hz), 129.6, 125.0, 123.3, 117.7, 81.7, 81.1 (d, *J* = 3.0 Hz), 77.5, 62.4 (d, *J* = 6.6 Hz), 62.3 (d, *J* = 6.6 Hz), 59.8, 58.9, 52.1, 38.6, 28.6, 28.5, 28.4 (d, *J* = 138.0 Hz), 16.6 (d, *J* = 6.0 Hz); IR (neat) 2979, 1715, 1481, 1391, 1366, 1252, 1155, 1023, 966 cm^{-1}; LRMS m/z calcd for $C_{31}H_{45}N_2O_{11}PNa$ $[M+Na]^+$ 675.3, found 675.3.



4.11

(2R,3aS,8aR)-1,8-di-tert-butyl 2-methyl 3a-((Z)-4-diazo-4-(diethoxyphosphoryl)-1-methoxy-1-oxobut-2-en-2-yl)-3,3a- dihydropyrrolo [2,3-b]indole-1,2,8(2H,8aH)-tricarboxylate (4.11). To a solution of phosphonate **4.10** (110 mg, 0.169 mmol) and tosyl azide (38 mg, 0.193 mmol) in CH_3CN (5 mL) was added DBU (30 mg, 0.20 mmol) dropwise at 0 °C. The reaction mixture was slowly brought to rt and stirred for 12h. Concentrate and flash chromatography (1:1 hexane/ethyl acetate) provided 56 mg of diazo **4.11** (49%) as an orange oil. **4.11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (br, 1H), 7.24 - 7.22 (m, 1H), 7.02 - 7.00 (m, 2H), 6.42 (s, 1H), 5.52 (m, 1H), 4.66 (m, 1H), 4.11 - 3.91 (m, 4H), 3.74 (m, 3H), 3.12 (s, 3H), 2.79 (dd, *J* = 12.7, 9.3 Hz, 1H), 2.64 (d, *J* = 12.7 Hz, 1H), 1.55 (s, 9H), 1.46 (br, 9H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.16 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 166.3, 152.5, 143.5, 132.4, 129.7, 126.6, 125.2, 124.2, 123.4, 117.9, 81.7, 81.6, 81.1, 77.5, 63.3 (d, *J* = 5.5 Hz), 59.9, 52.1, 51.9 (d, *J* = 242.7 Hz), 51.7, 38.8, 28.6, 28.5, 16.3 (d, *J* = 6.6 Hz), 16.2 (d, *J* = 7.1 Hz); IR (neat) 2979, 2361, 2094, 1760, 1708, 1601, 1392, 1156, 1017 cm^{-1}; LRMS m/z calcd for $C_{31}H_{43}N_4O_{11}PNa$ $[M+Na]^+$ 701.3, found 700.8.

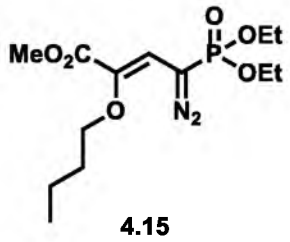


4.12

(2R,3aS,8aR)-1,8-di-tert-butyl 2-methyl 3a-(5-(diethoxyphosphoryl)-2-methoxyfuran-3-yl)-3,3a-dihydropyrrolo [2,3-b]indole-1,2,8(2H,8aH)-tricarboxylate (4.12). To a solution of diazo **4.11** (38 mg, 0.056 mmol) in CH_2Cl_2

(3 mL) at rt was added $Cu(CH_3CN)_4PF_6$ (1.0 mg, 2.7 μmol) in one portion. The reaction mixture was stirred at rt for 24h. Concentrate and flash chromatography (1:2 hexane:ethyl acetate) provided 23 mg of furan **4.12** (64%) as a colorless oil.

4.12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (br, 1H), 7.20 (t, *J* = 6.7 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.76 (br, 1H), 6.28 (br, 1H), 4.60 (br, 1H), 4.15 - 3.97 (m, 4H), 3.94 (s, 3H), 3.13 (s, 3H), 2.90 - 2.79 (m, 2H), 1.56 (s, 9H), 1.44 (br, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.8 (d, *J* = 11.6 Hz), 142.6, 134.2, 132.0 (d, *J* = 252.8 Hz), 129.1, 125.8 (d, *J* = 22.2 Hz), 123.9 (d, *J* = 21.7 Hz), 118.0, 110.1, 100.6, 81.8, 81.7, 81.1, 77.5, 62.9, 59.8, 58.6, 52.1, 37.4, 28.5, 28.5, 16.5 (d, *J* = 3.5 Hz), 16.4 (d, *J* = 3.5 Hz); IR (neat) 2979, 1761, 1702, 1623, 1479, 1391, 1152, 1016 cm^{-1}; LRMS m/z calcd for $C_{31}H_{43}N_2O_{11}PNa$ $[M+Na]^+$ 673.3, found 672.9.

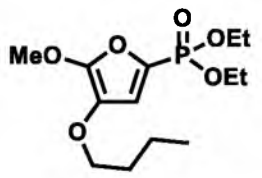


4.15

(Z)-methyl 2-butoxy-4-diazo-4-(diethoxyphosphoryl)but-2-enoate (4.15). To a solution of phosphonate **4.14** (0.362 g, 1.17 mmol) and ABSA (0.310 g, 1.29 mmol) in CH_3CN (10 mL) was added DBU (0.214 g, 1.41 mmol) dropwise at 0 °C. The reaction mixture was slowly brought to rt and stirred for 12h at rt. Concentrate and flash chromatography (2:1 hexane/ethyl acetate) provided 0.312 g of diazo **4.15** (79%) as an orange oil.

4.15: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07 (d, *J* = 7.3 Hz, 1H), 4.19 - 4.07 (m, 4H), 3.83 (t, *J* = 6.8 Hz, 2H), 3.74 (s, 3H), 1.65 - 1.60 (m, 2H), 1.41 - 1.33 (partially

obscure, m, 2H), 1.34 (t, *J* = 7.3 Hz, 6H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 140.3 (d, *J* = 10.6 Hz), 112.6 (d, *J* = 12.1 Hz), 63.3 (d, *J* = 5.5 Hz), 52.0, 49.3 (d, *J* = 229.1 Hz), 31.3, 19.1, 16.3 (d, *J* = 7.1 Hz), 14.0; IR (neat) 2959, 2874, 2086, 1717, 1618, 1257, 1094, 1018, 971 cm^{-1}; LRMS m/z calcd for $C_{13}H_{23}N_2O_6PNa$ $[M+Na]^+$ 357.3, found 357.2.



4.16

Diethyl 4-butoxy-5-methoxyfuran-2-ylphosphonate (4.16). To a solution of $Rh_2(Oct)_4$ in CH_2Cl_2 was added a solution of diazo **4.15** in CH_2Cl_2 via syringe pump within 2h at rt. The reaction mixture was stirred for another 2h at rt. Concentrate and chromatography (1:1 hexane:ethyl acetate, SiO_2 was neutralized with 1% NEt_3) provided 23 mg of furan **4.16** (70%) as a colorless oil. **4.16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.15 - 7.14 (m, 1H), 4.05 - 3.84 (m, 4H), 3.53 (t, *J* = 6.5 Hz, 2H), 3.42 (s, 3H), 1.39 (quintet, *J* = 7.0 Hz, 2H), 1.20 (sixtet, *J* = 7.3 Hz, 2H), 0.99 (t, *J* = 7.0 Hz, 6H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5 (d, *J* = 8.4 Hz), 131.4 (d, *J* = 249.4 Hz), 125.1 (d, *J* = 11.5 Hz), 119.3 (d, *J* = 22.3 Hz), 72.0, 61.9 (d, *J* = 5.4 Hz), 59.0, 31.4, 18.9, 15.9 (d, *J* = 6.1 Hz), 13.5; IR (neat) 2960, 2874, 1751, 1645, 1516, 1257, 1016, 959 cm^{-1}; LRMS m/z calcd for $C_{13}H_{24}O_6P$ $[M+H]^+$ 307.2, found 307.1.

4.5 References

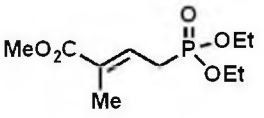
1. Espejo, V. R.; Li, X.; Rainier, J. D. *J. Am. Chem. Soc.*, **2010**, *132*, 8282.

2. Wang, J.; Boyarskikh, V. Rainier, J. D. *Org. Lett.* **2011**, *13*, 700

3. Gómez-Galeno, G. E.; Dang, Q.; Nguyen, T. H.; Boyer, S. H.; Grote, M. P.; Sun, Z.; Chen, M.; Craigo, W. A.; van Poelje, P. D.; MacKenna, D. A.; Cable, E. E.; Rolzin, P. A.; Finn, P. D.; Chi, B.; Linemeyer, D. L.; Hecker, S. G.; Erion, M. D. *ACS Med. Chem. Lett.* **2010**, *1*, 478.

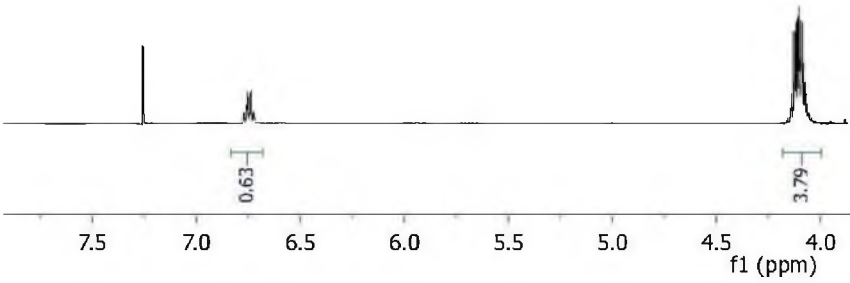
APPENDIX

H AND ^{13}C NMR SPECTRA

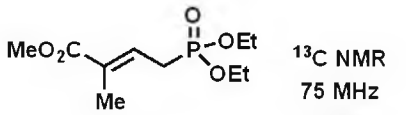


2.47

^{1}H NMR
300 MHz
$CDCl_3$

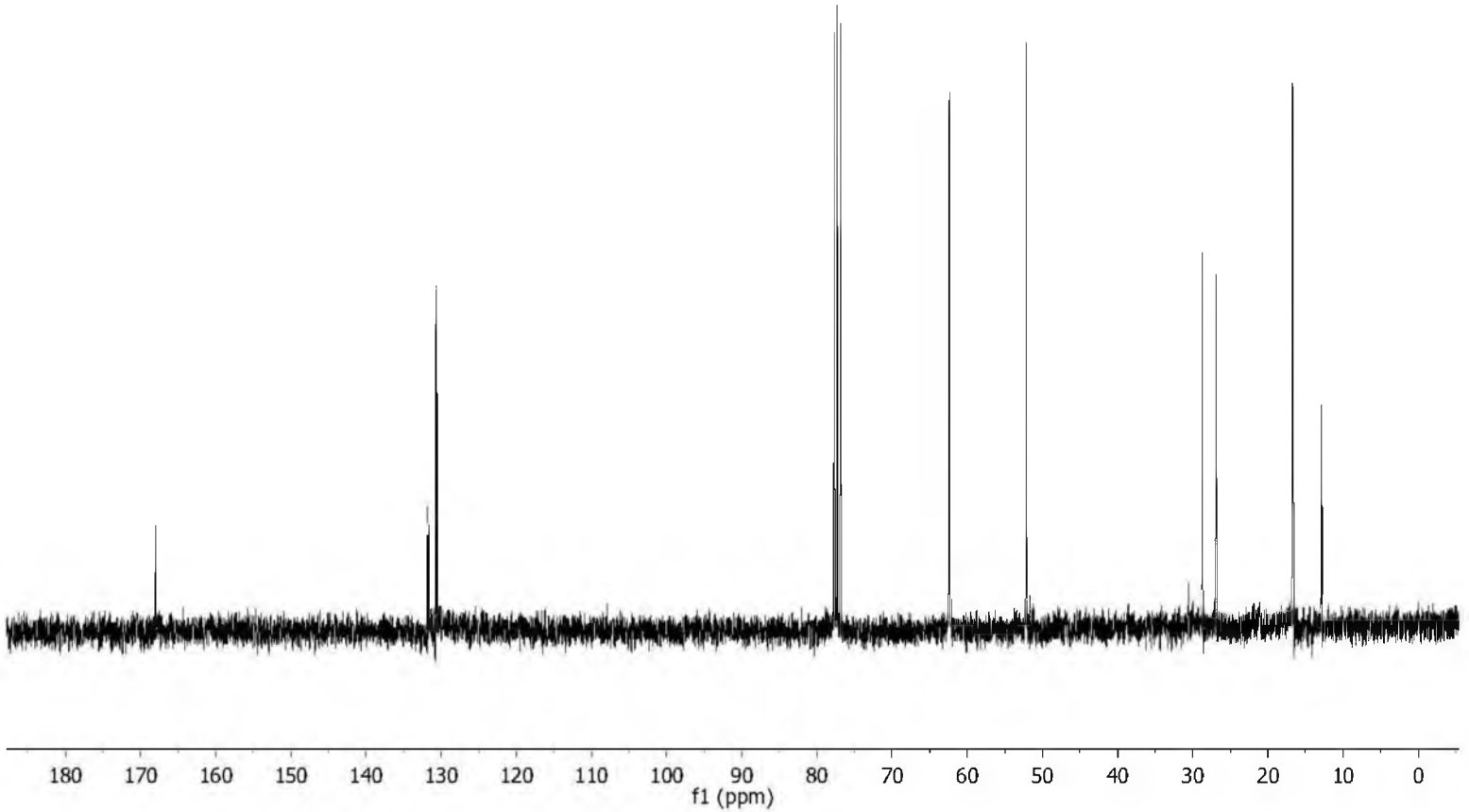


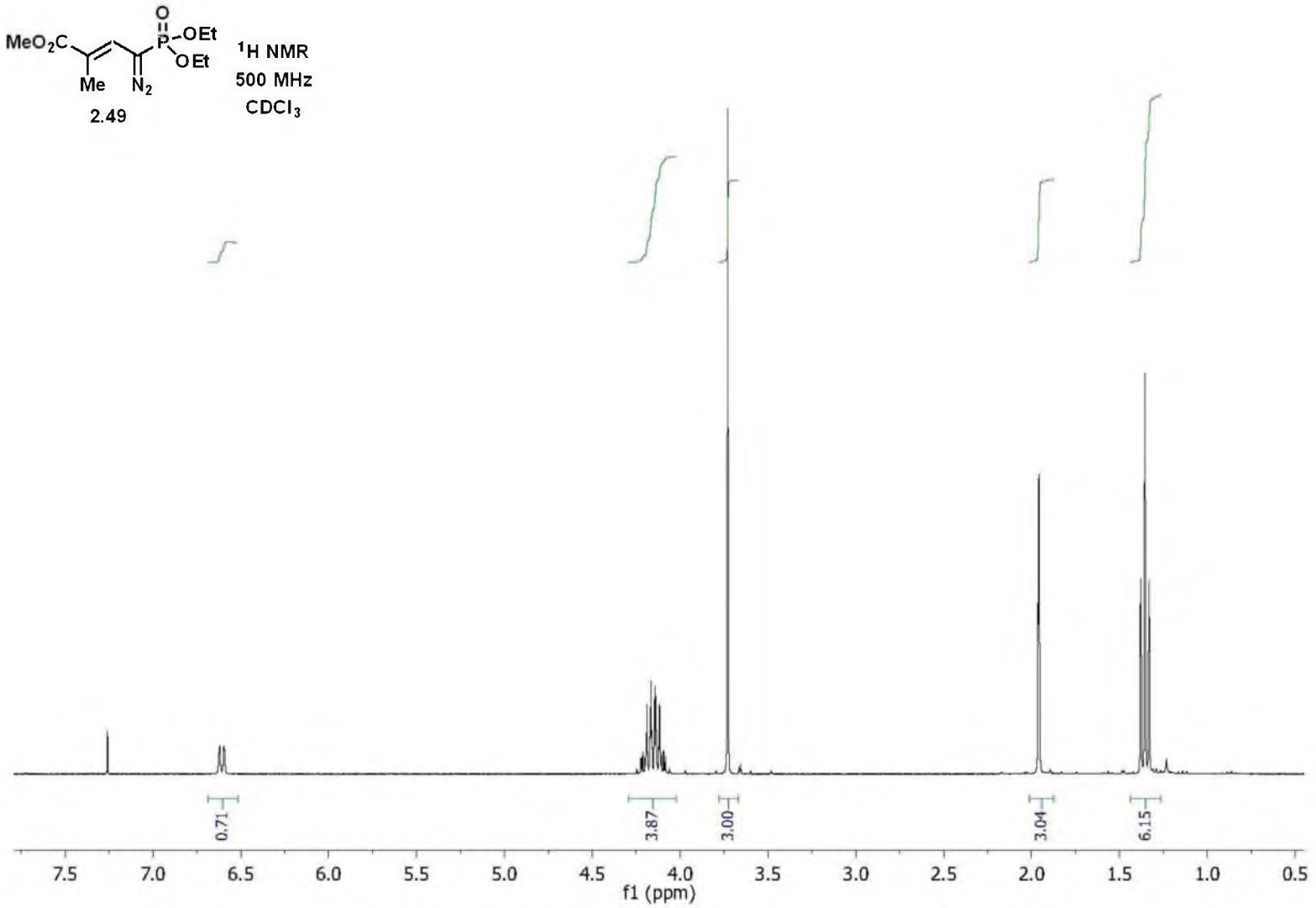
3.00
1.81
2.72
6.62
3.5
3.0
2.5
2.0
1.5
1.0

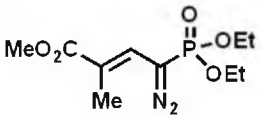


2.47

^{13}C NMR
75 MHz
$CDCl_3$

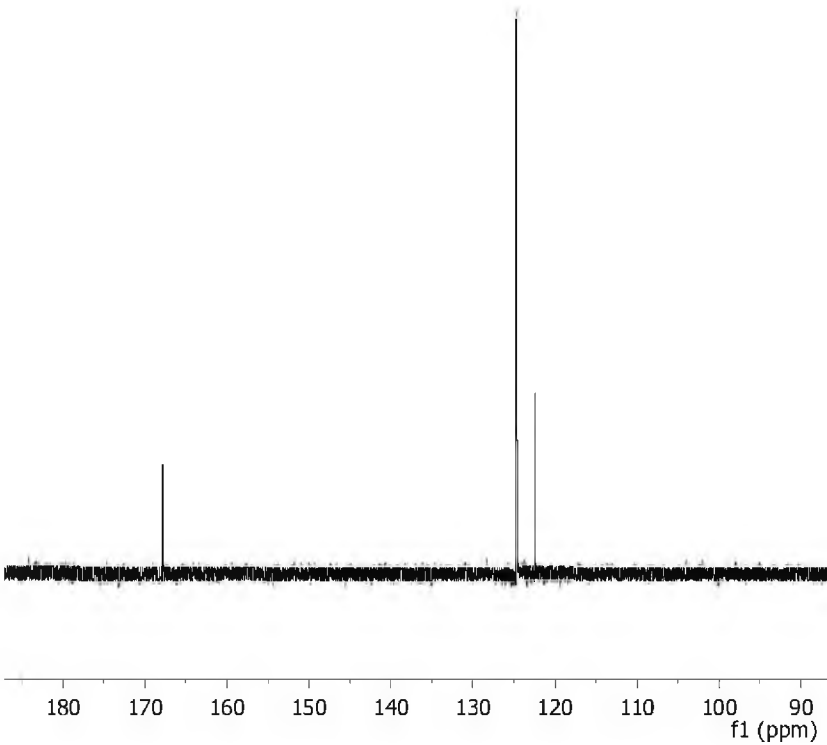


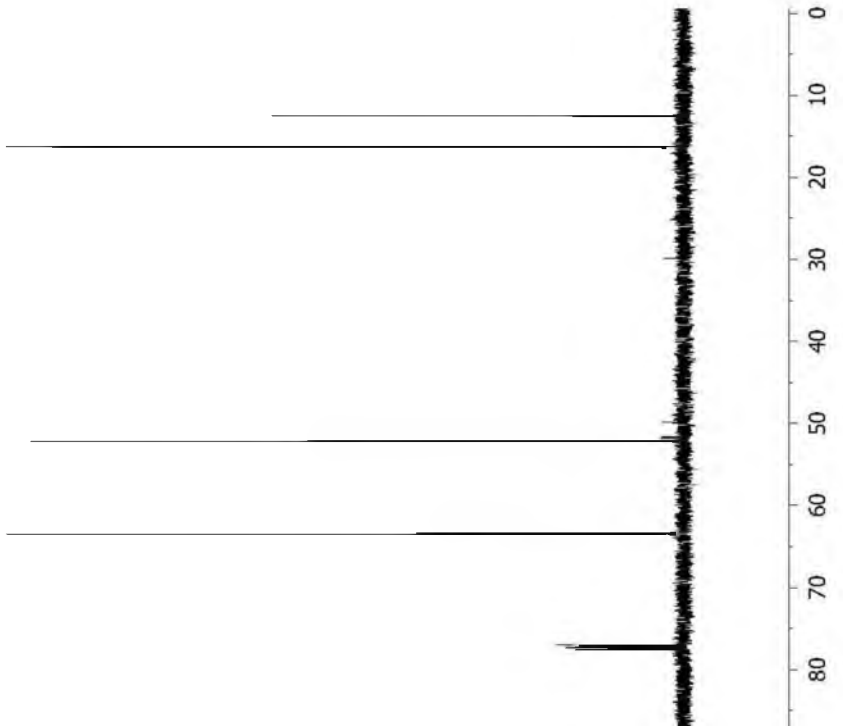

MeO2C
Me
N2
P
O
OEt
OEt
2.49
1H NMR
500 MHz
CDCl3
0.71
3.87
3.00
3.04
6.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

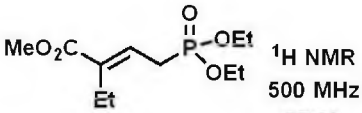


2.49

^{13}C NMR
125 MHz
$CDCl_3$

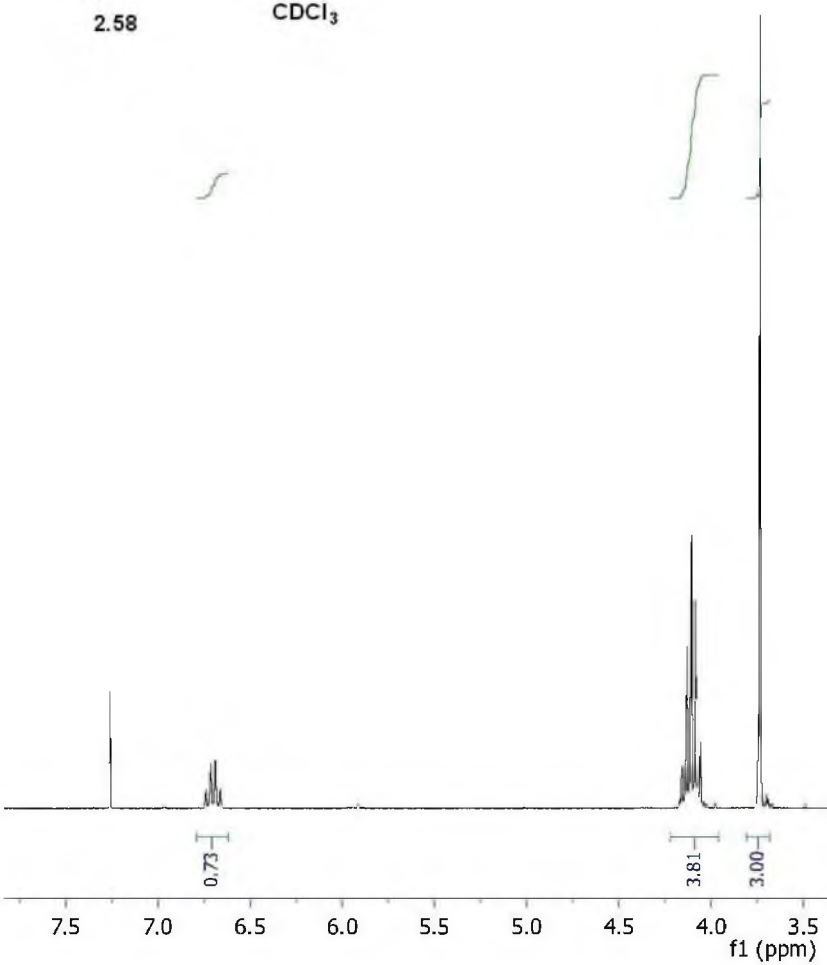


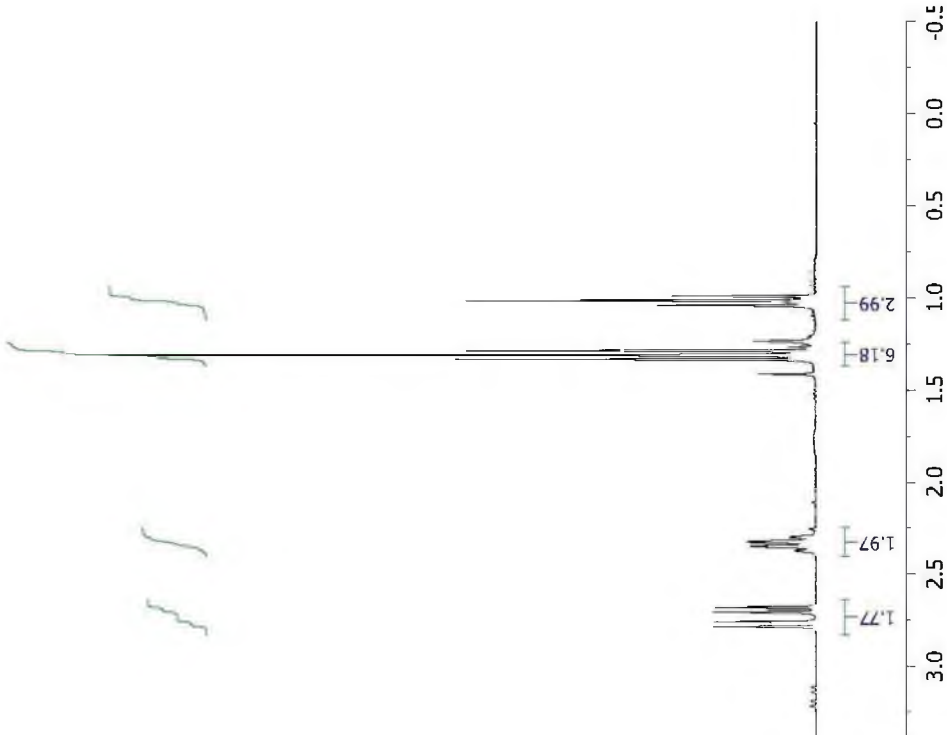

0
10
20
30
40
50
60
70
80

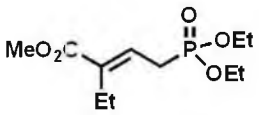


2.58

^{1}H NMR
500 MHz
$CDCl_3$

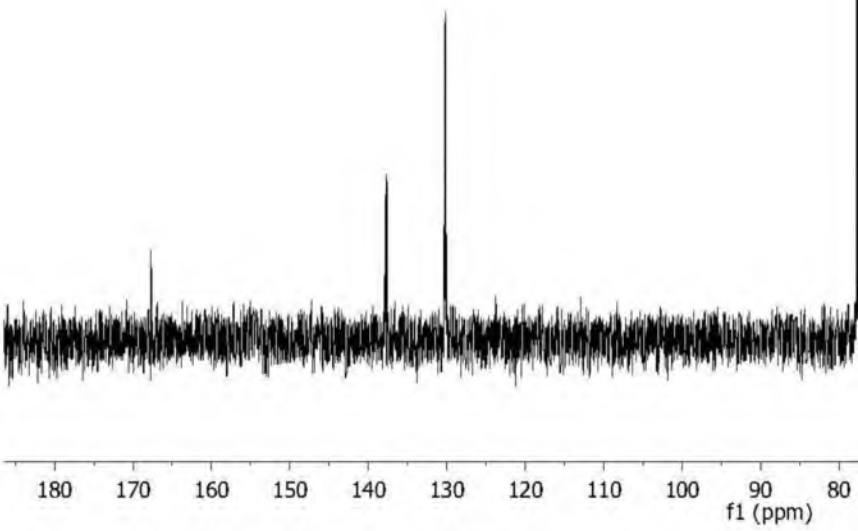


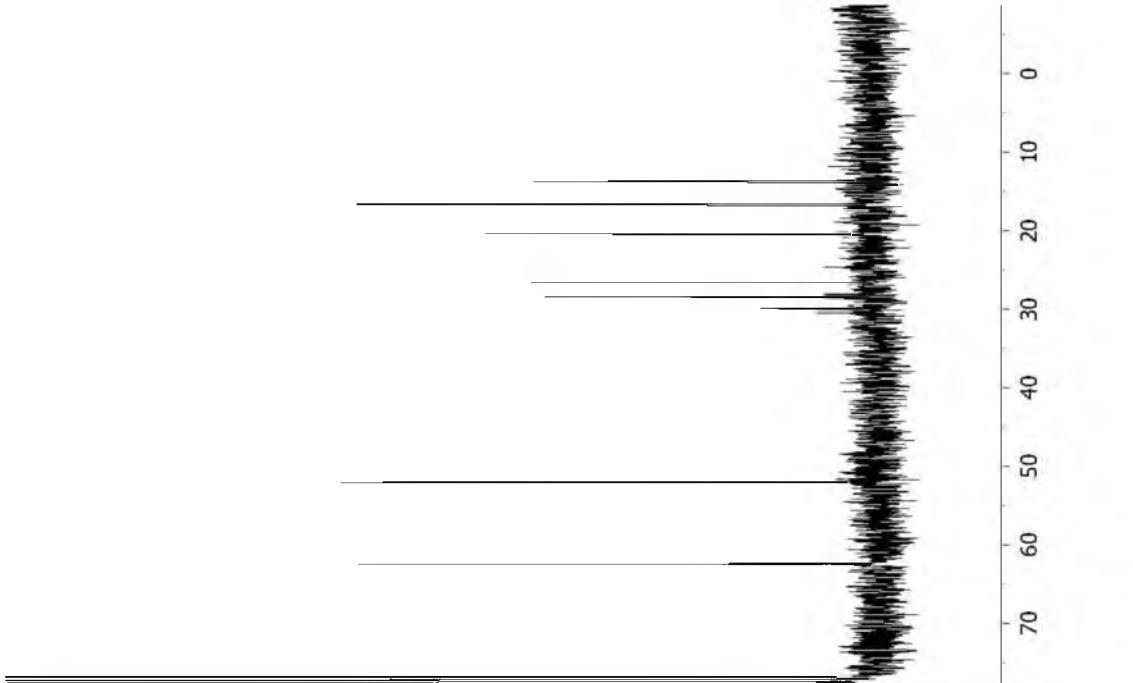

2.99
6.18
1.97
1.77
3.0
2.5
2.0
1.5
1.0
0.5
0.0

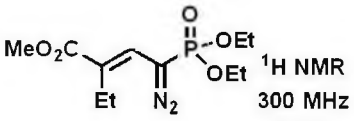


2.58

^{13}C NMR
125 MHz
$CDCl_3$

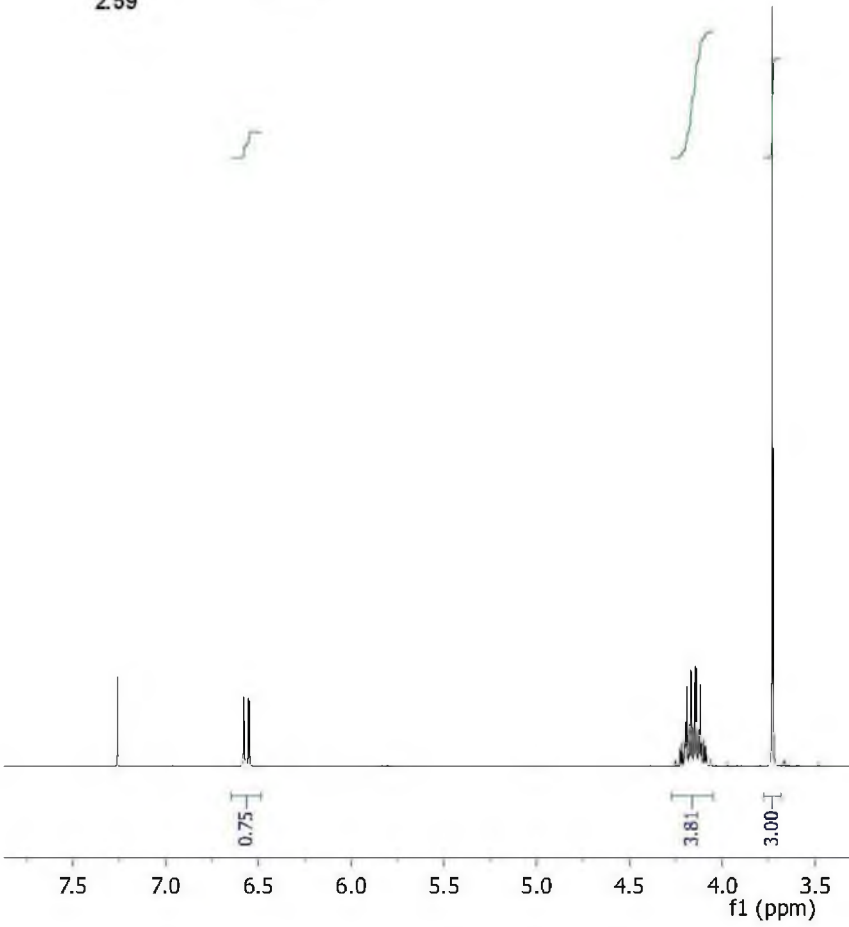


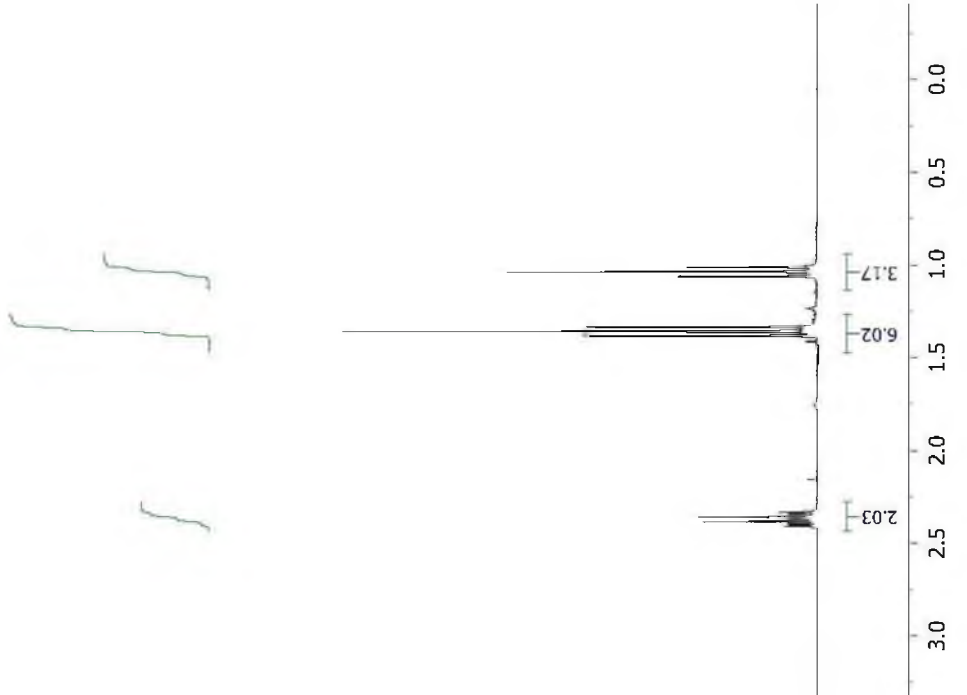

0
10
20
30
40
50
60
70

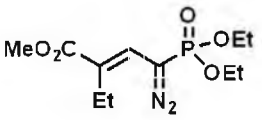


2.59

^{1}H NMR
300 MHz
$CDCl_3$

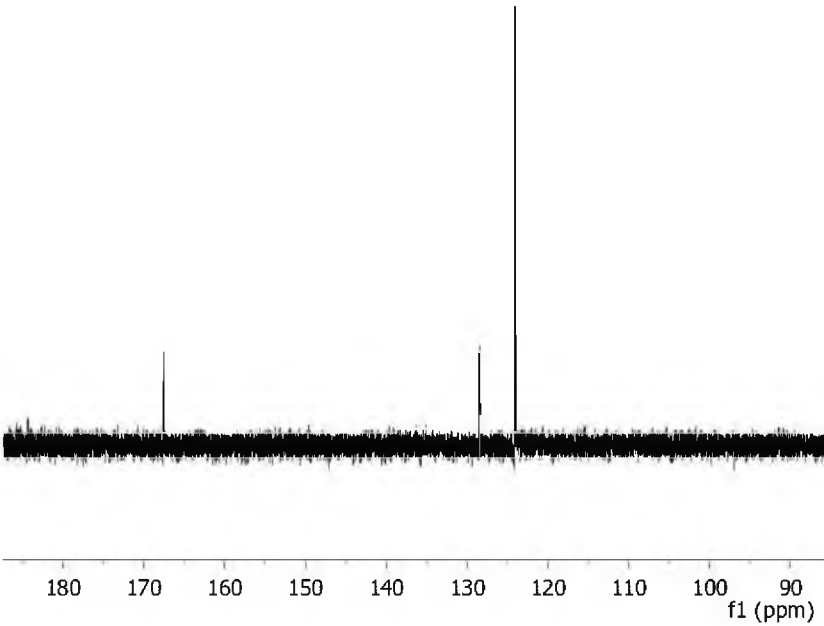


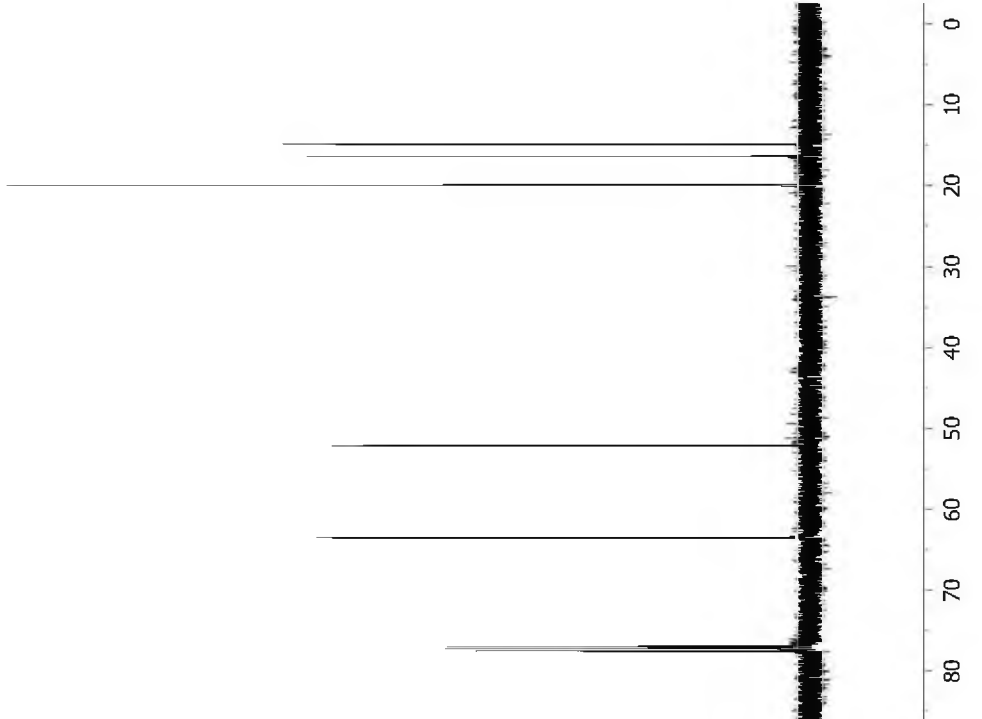

3.17
6.02
2.03
0.0
0.5
1.0
1.5
2.0
2.5
3.0

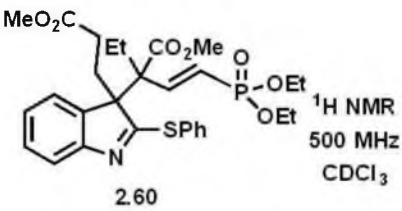


2.59

^{13}C NMR
125 MHz
$CDCl_3$

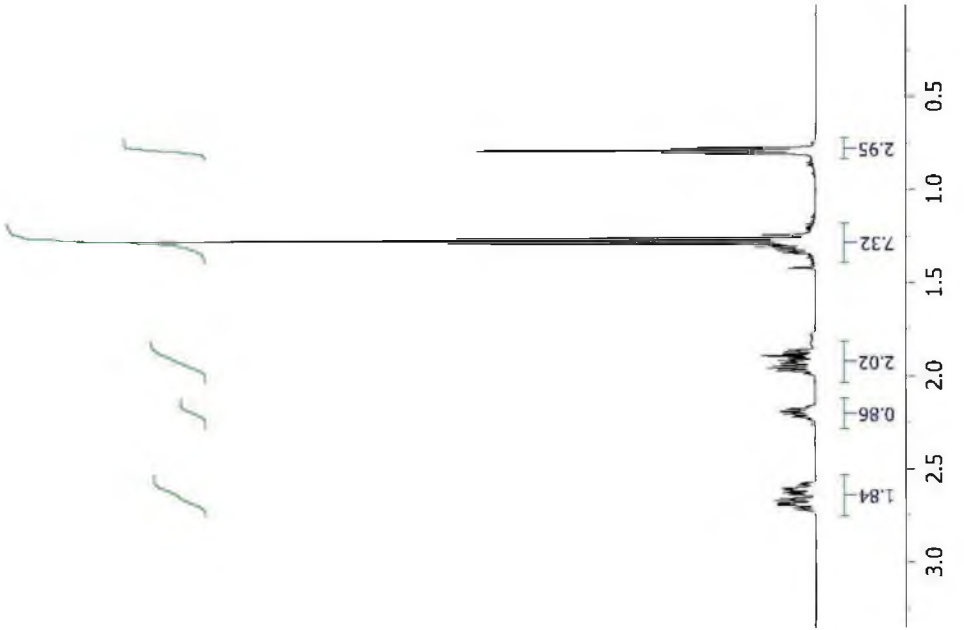


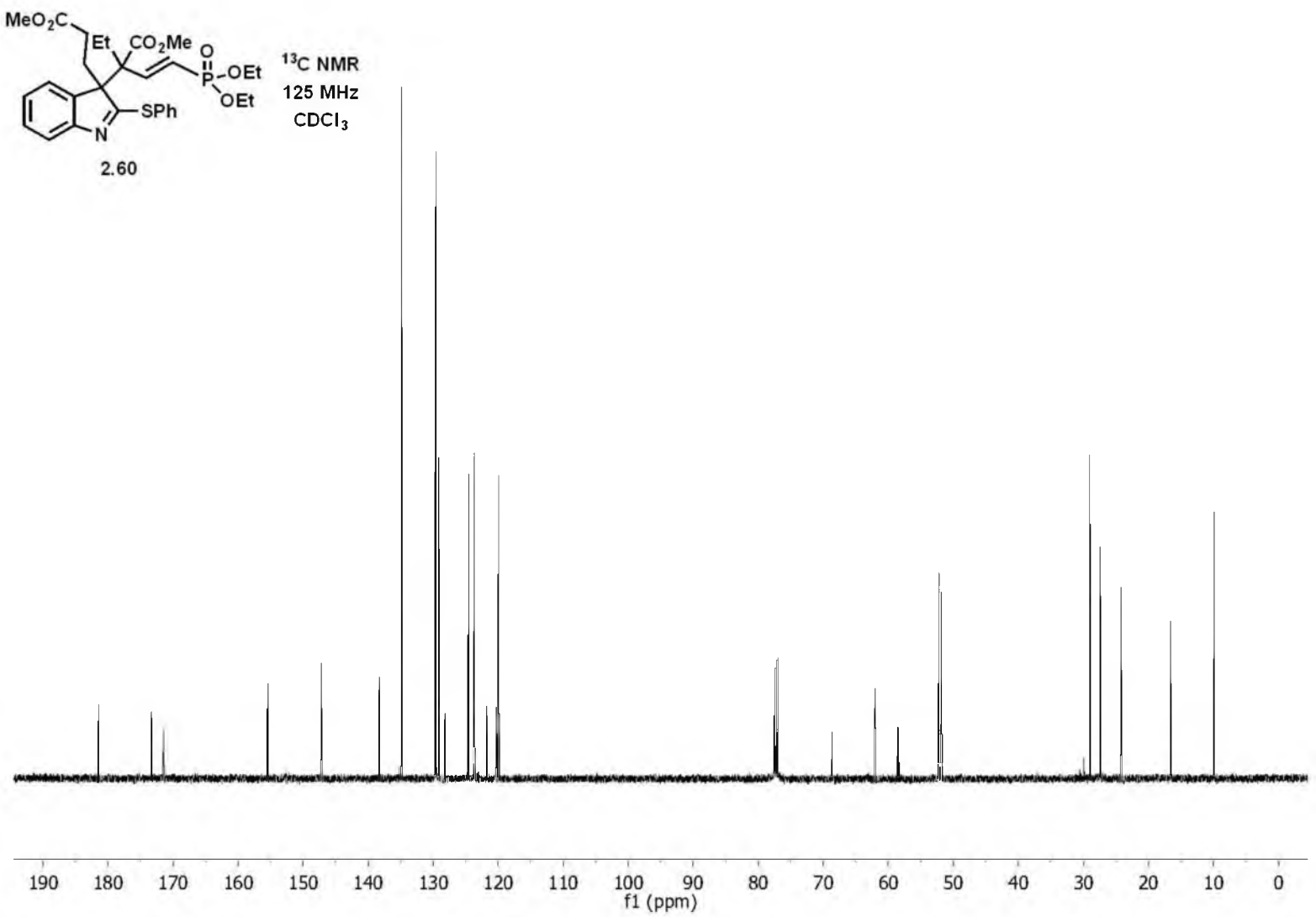

0
10
20
30
40
50
60
70
80

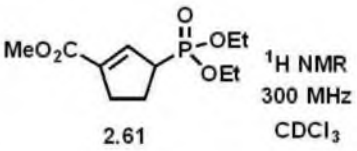


2.60

^{1}H NMR
500 MHz
$CDCl_3$

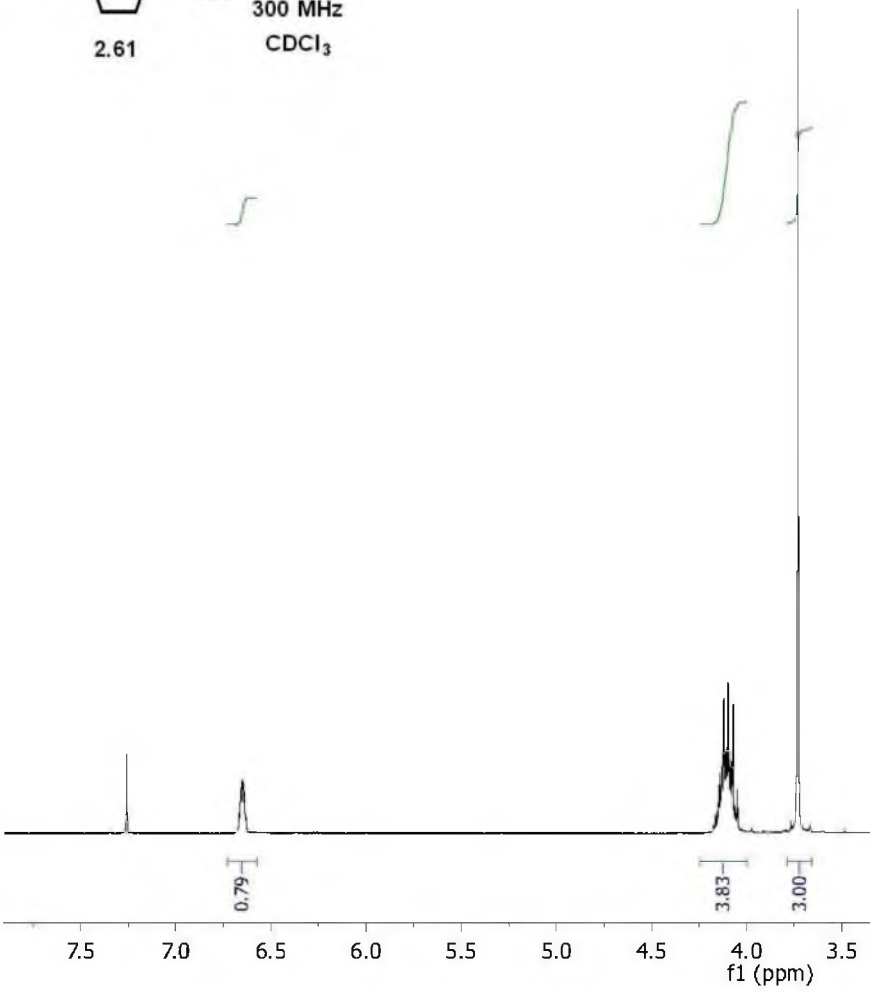

2.95
7.32
2.02
0.86
1.84
0.5
1.0
1.5
2.0
2.5
3.0

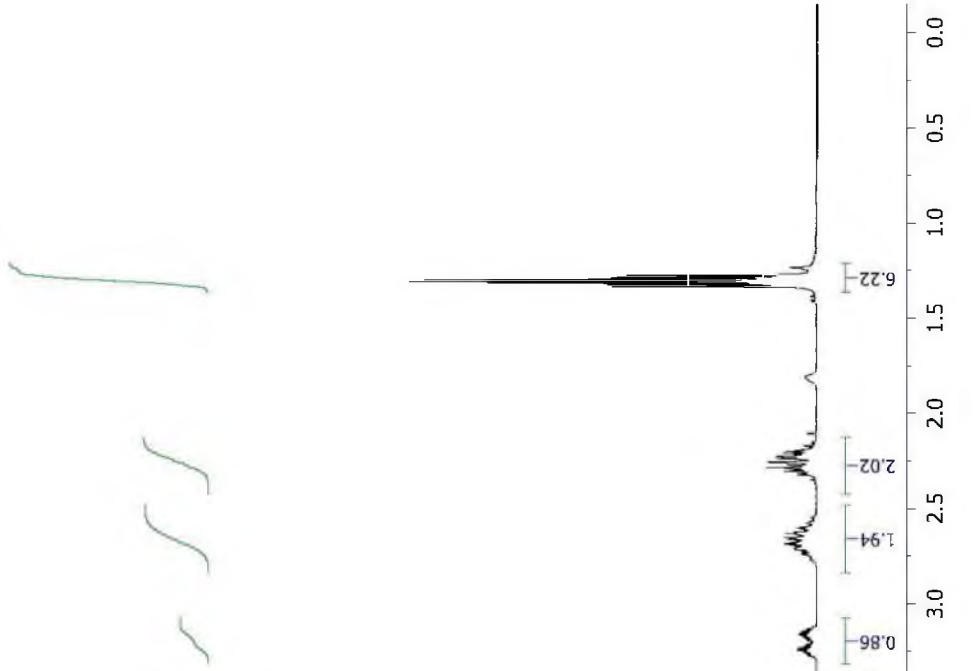

MeO2C
Et
CO2Me
O
P
OEt
OEt
SPh
N
2.60
13C NMR
125 MHz
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

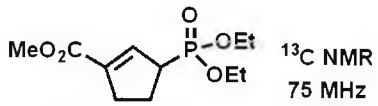


2.61

^{1}H NMR
300 MHz
$CDCl_3$

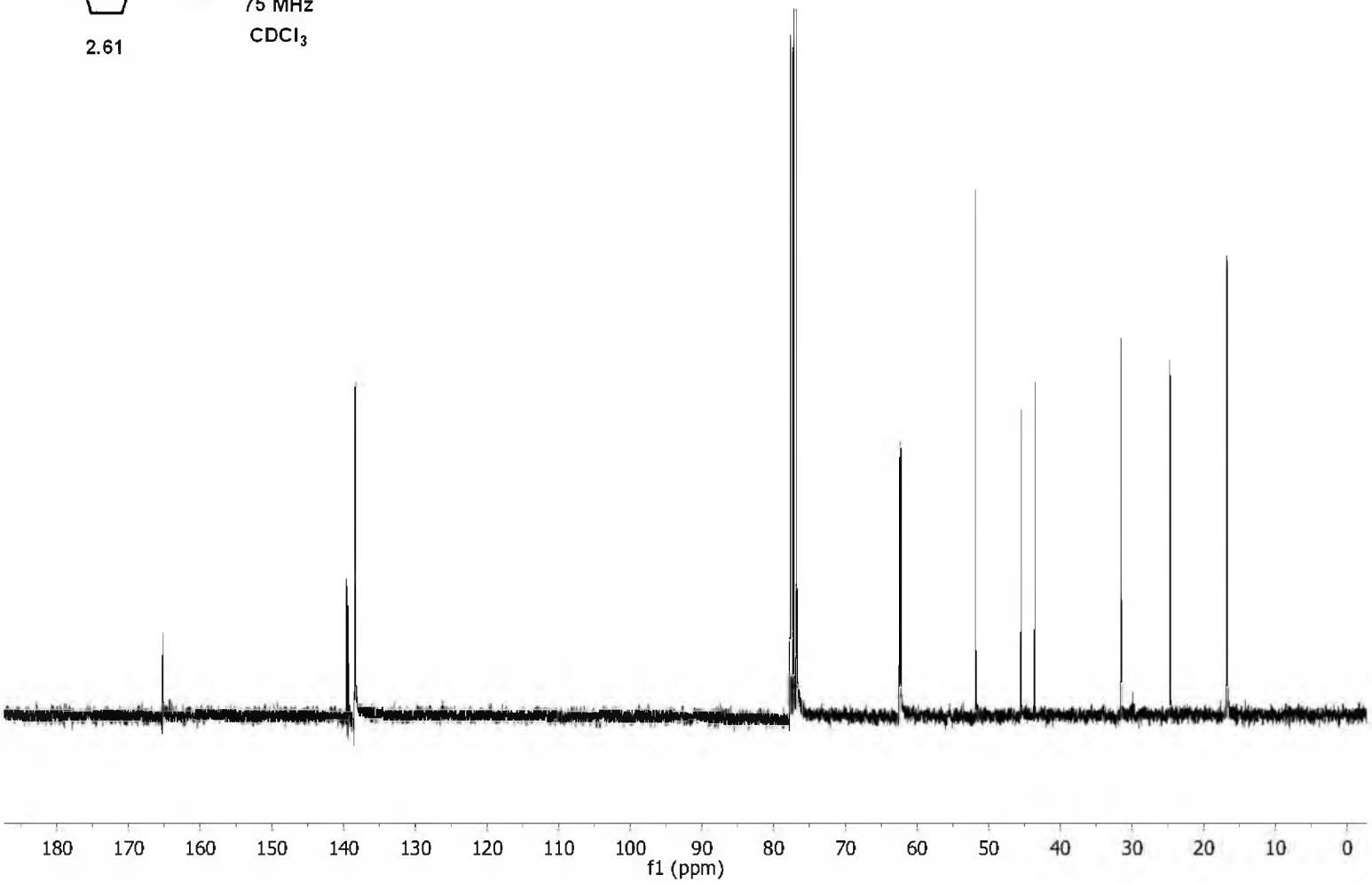


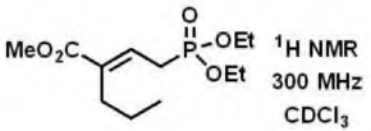

6.22
2.02
1.94
0.86
0.0
0.5
1.0
1.5
2.0
2.5
3.0



2.61

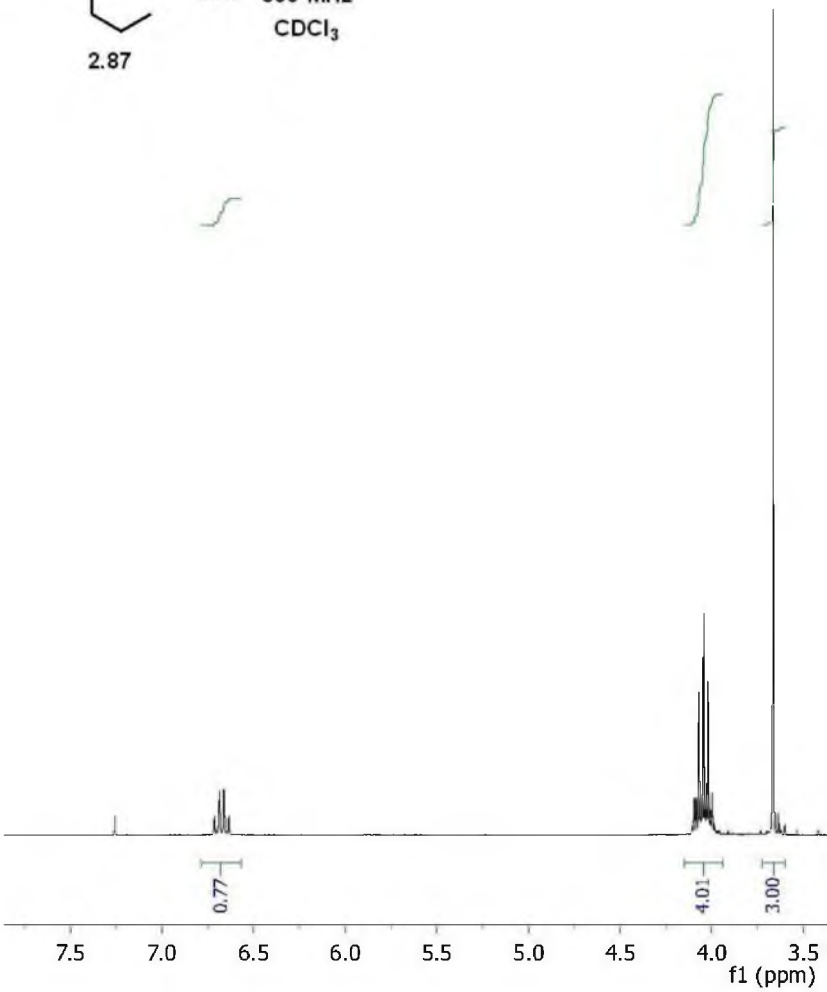
^{13}C NMR
75 MHz
$CDCl_3$

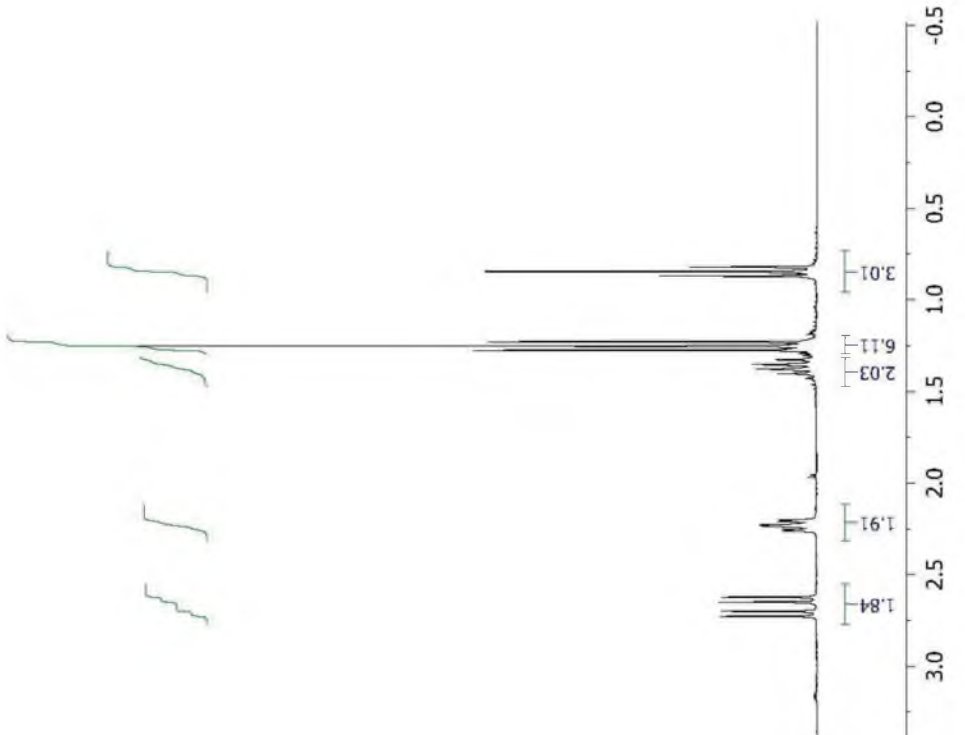


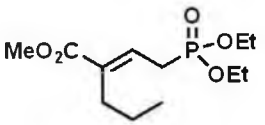


2.87

^{1}H NMR
300 MHz
$CDCl_3$

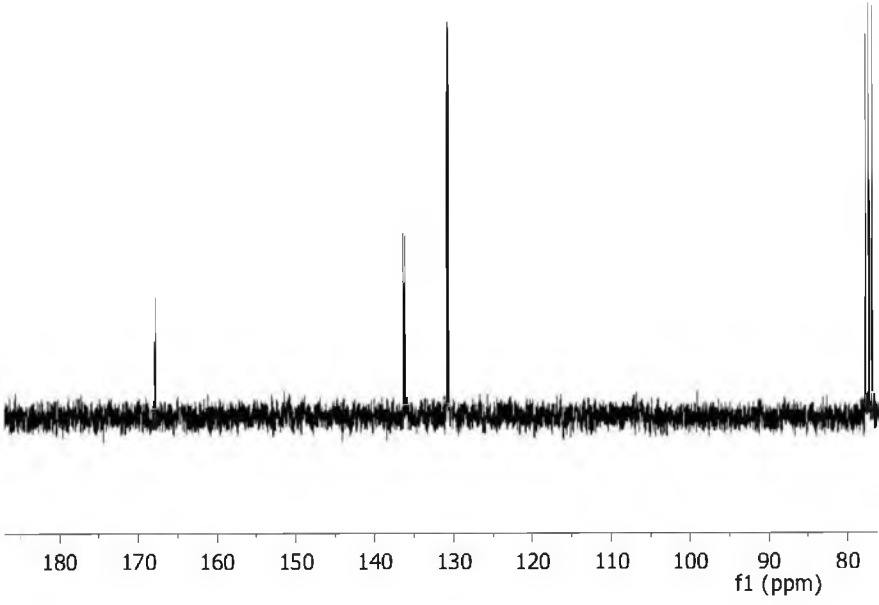


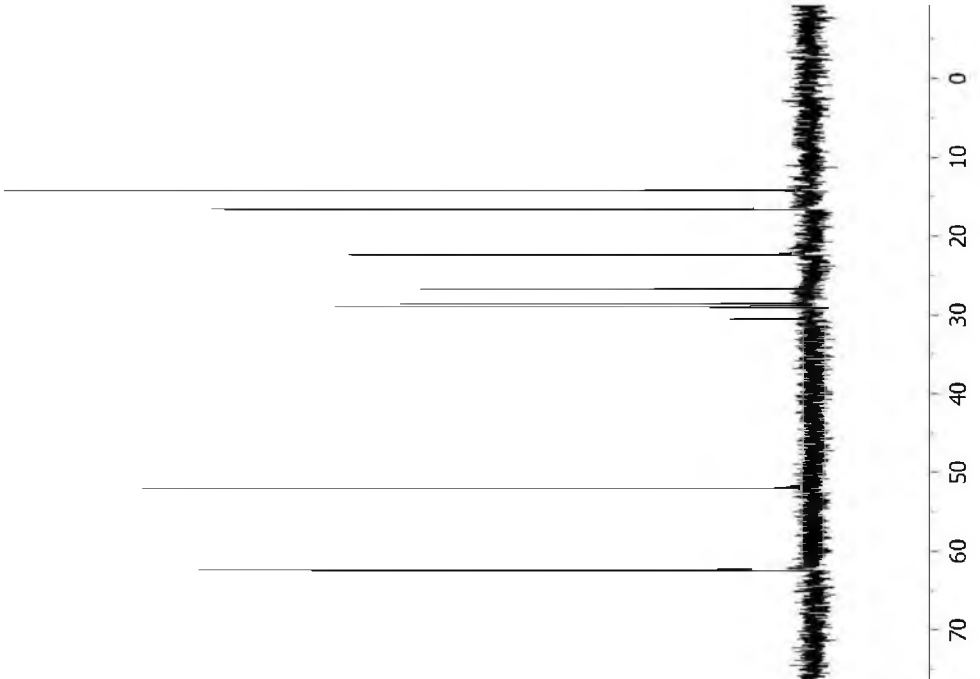

3.01
6.11
2.03
1.91
1.84
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0

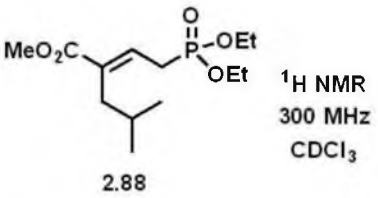


2.87

^{13}C NMR
75 MHz
$CDCl_3$

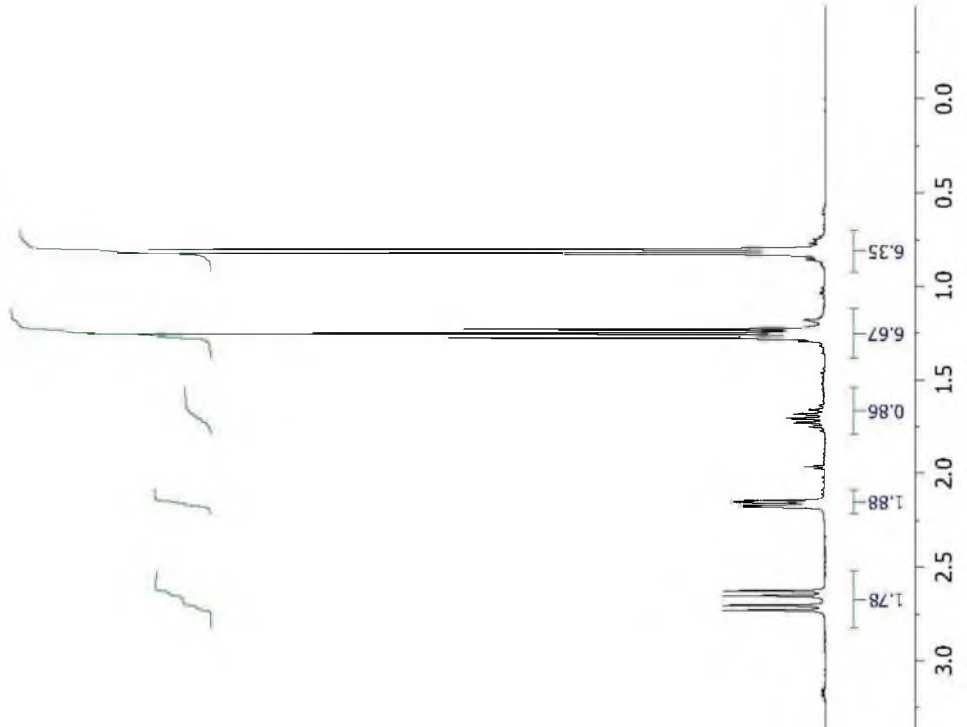


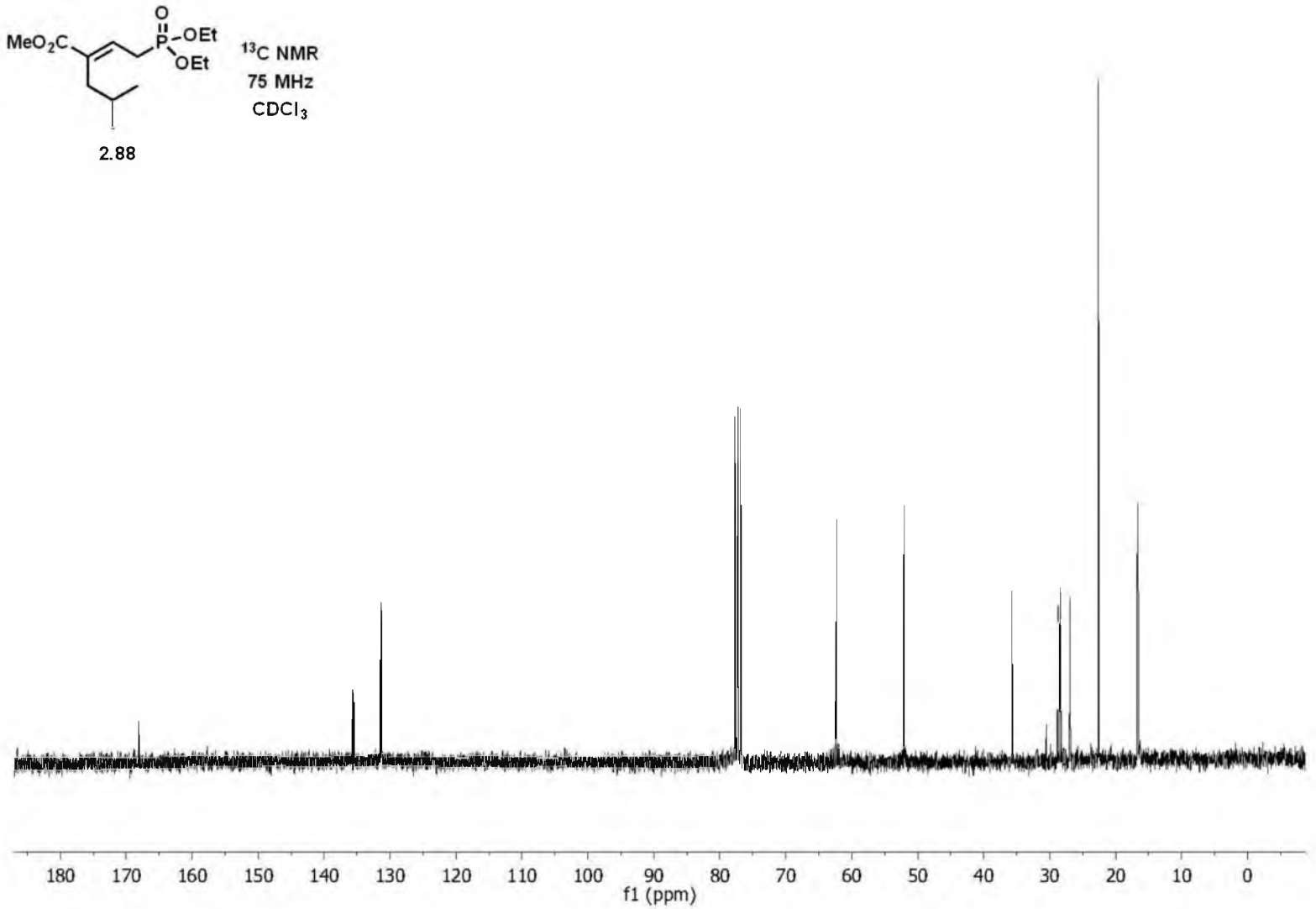

0
10
20
30
40
50
60
70

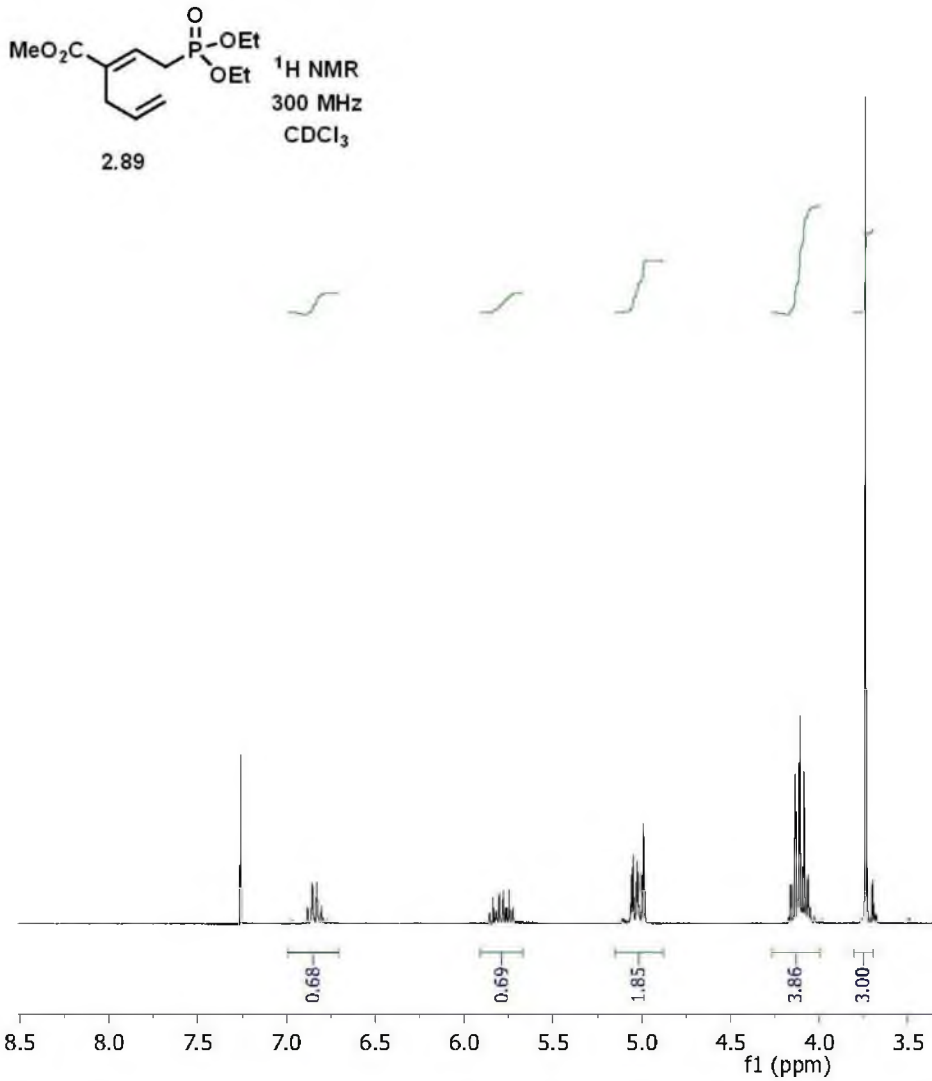


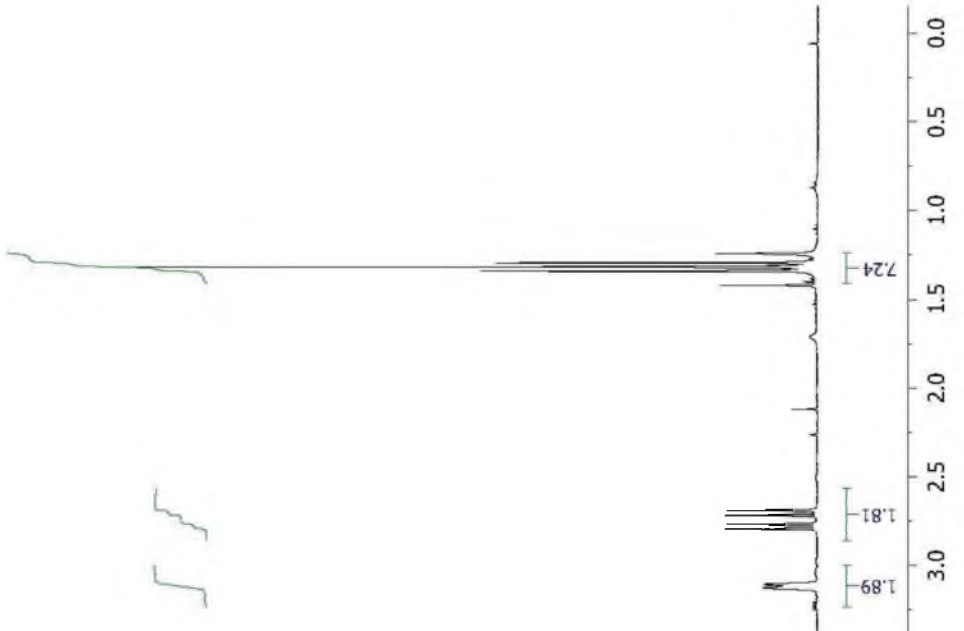
2.88

^{1}H NMR
300 MHz
$CDCl_3$


6.35
6.67
0.86
1.88
1.78
0.0
0.5
1.0
1.5
2.0
2.5
3.0


MeO2C
O
P
OEt
OEt
13C NMR
75 MHz
CDCl3
2.88
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MeO2C
O
P
OEt
OEt
2.89
1H NMR
300 MHz
CDCl3
0.68
0.69
1.85
3.86
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)


7.24
1.81
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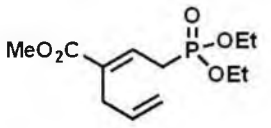
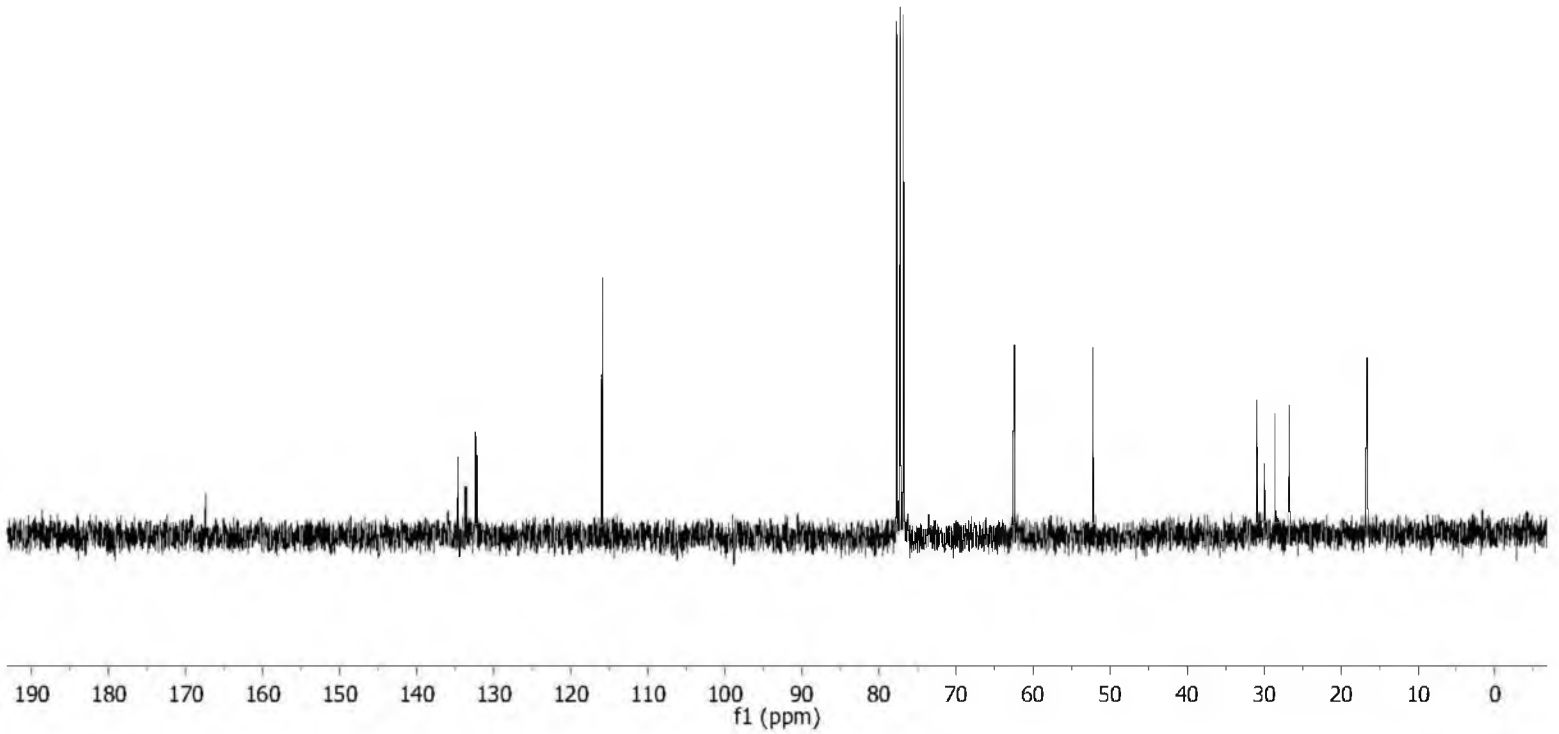
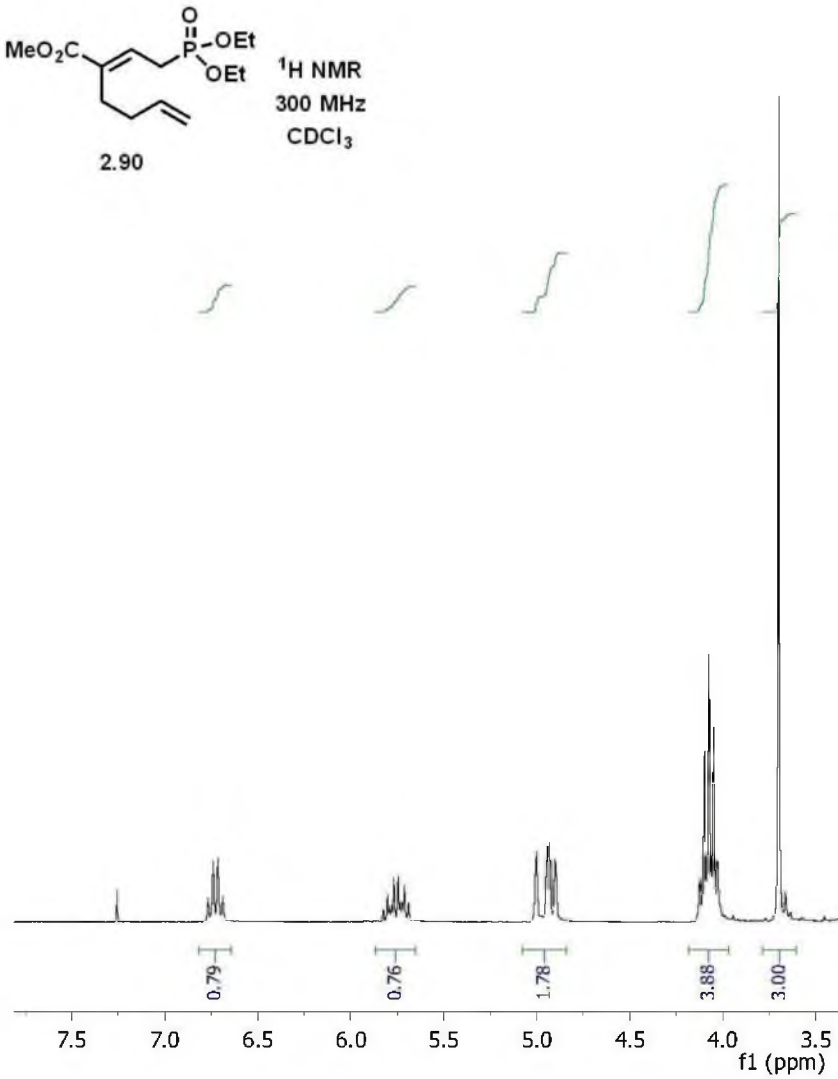
0.0
0.5
1.0
1.5
2.0
2.5
3.0

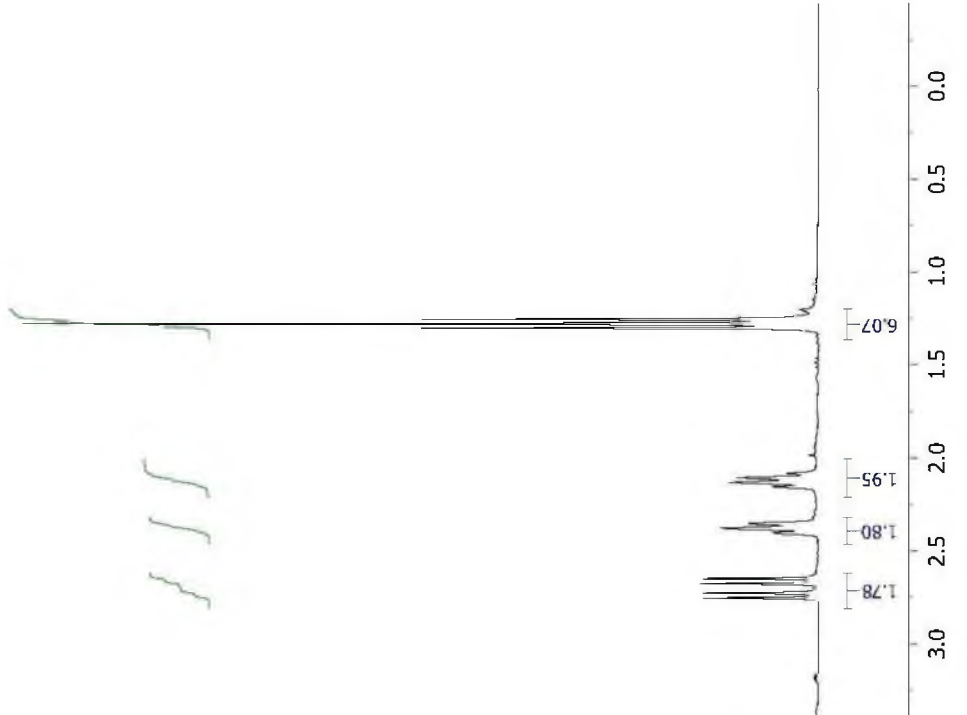


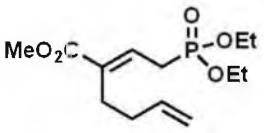
2.89

^{13}C NMR
75 MHz
$CDCl_3$



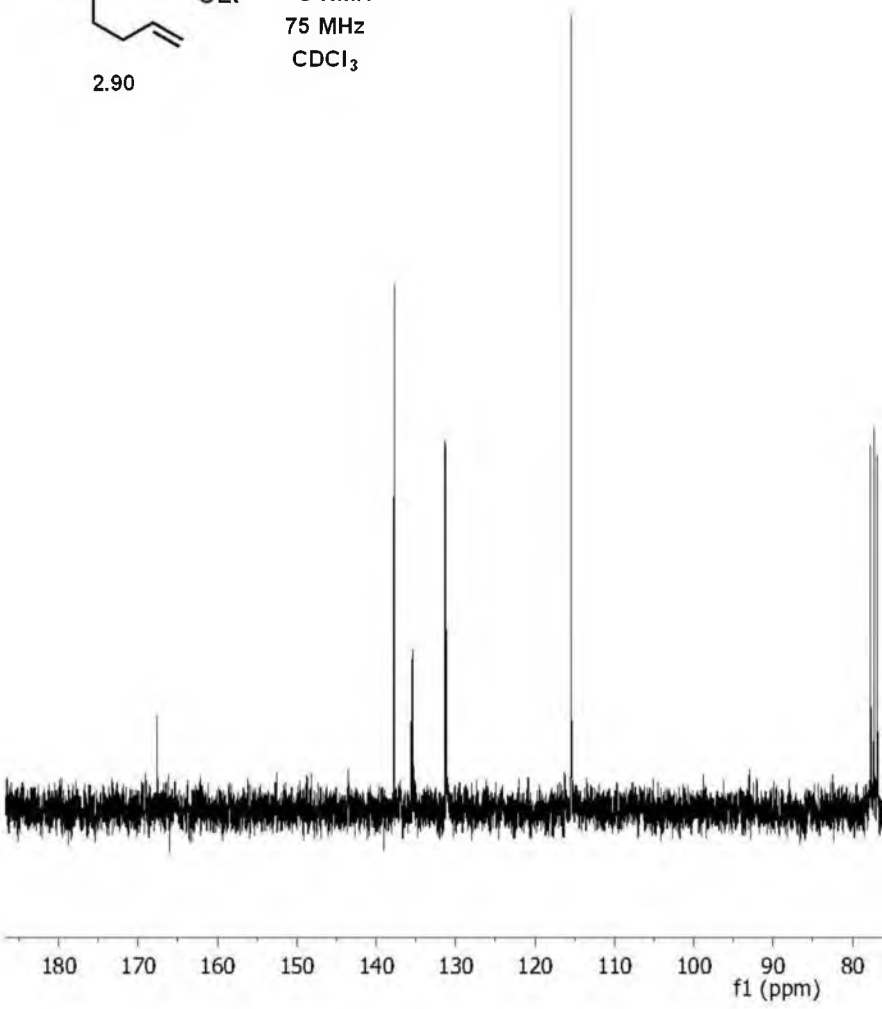

MeO2C
O
P
OEt
OEt
2.90
1H NMR
300 MHz
CDCl3
0.79
0.76
1.78
3.88
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

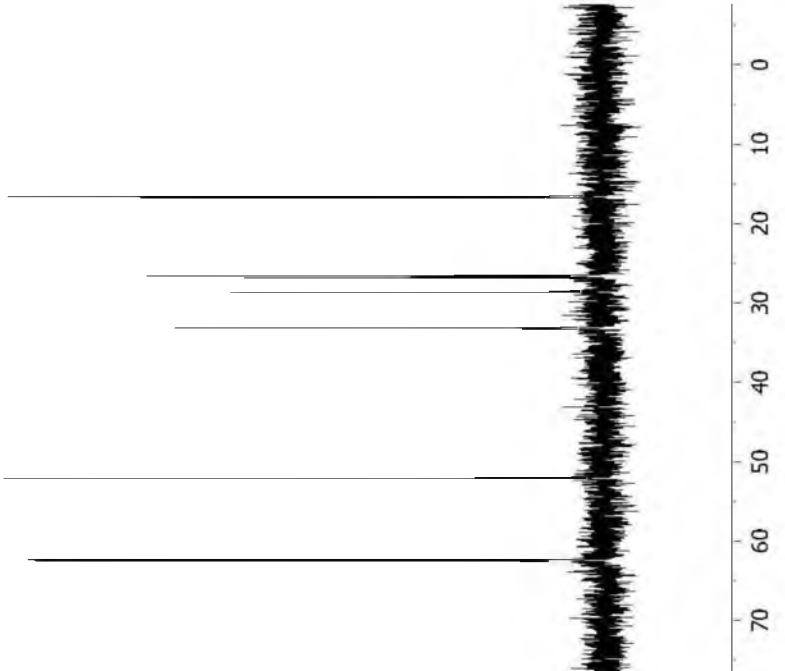

6.07
1.95
1.80
1.78
3.0
2.5
2.0
1.5
1.0
0.5
0.0

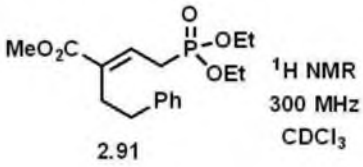


2.90

^{13}C NMR
75 MHz
$CDCl_3$

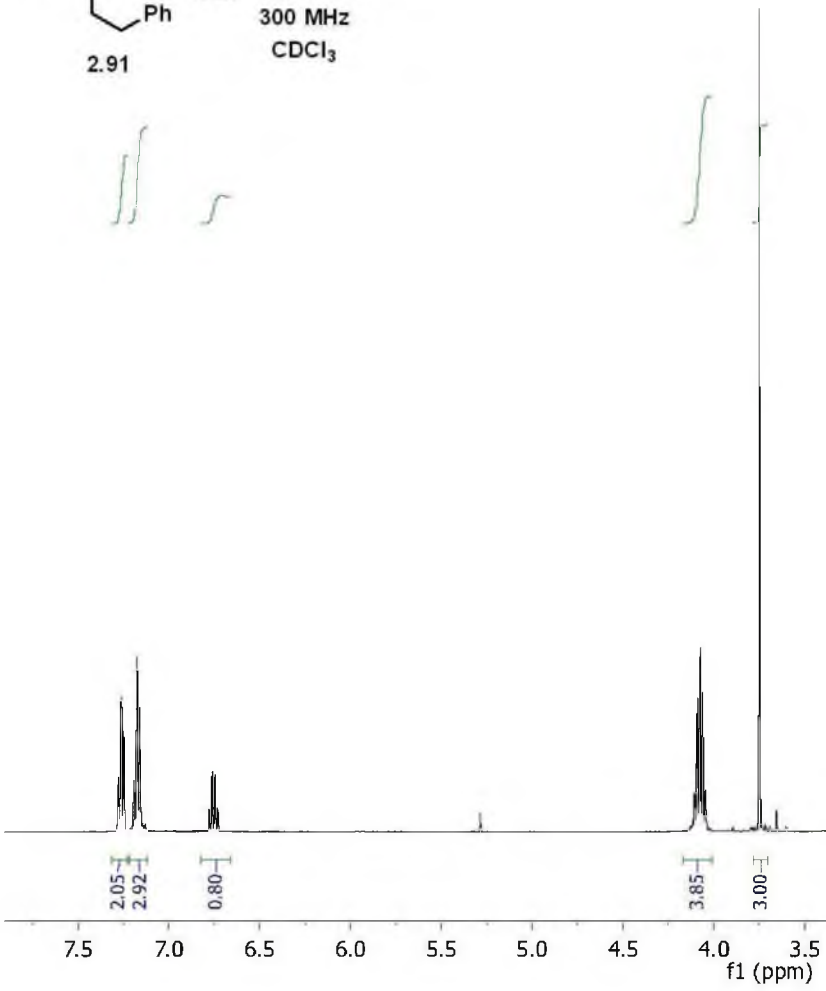


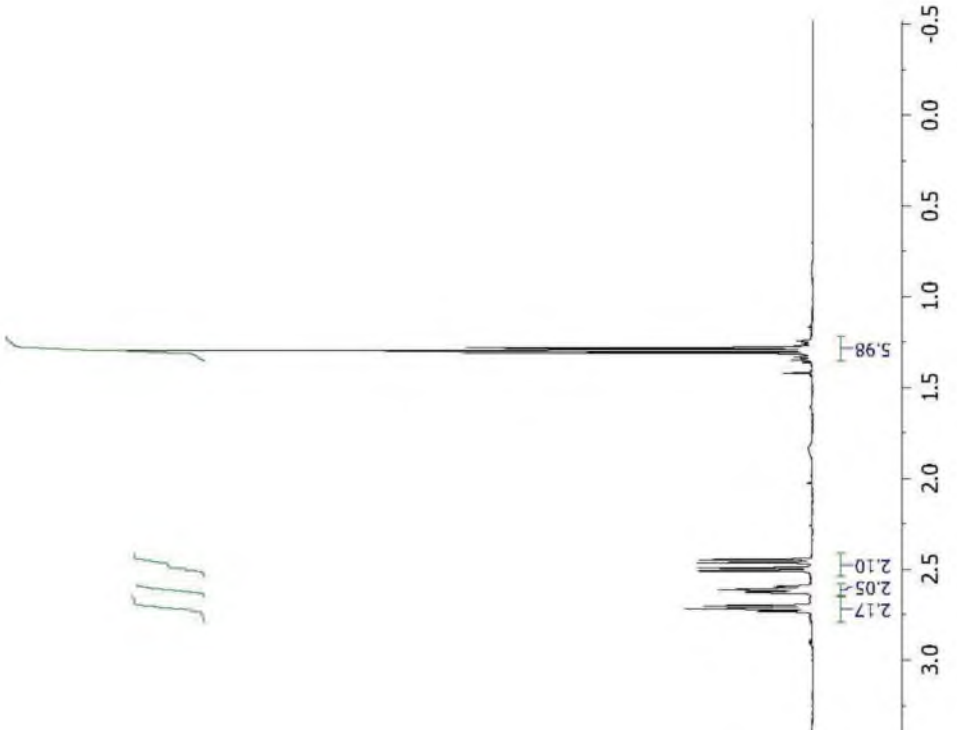

0
10
20
30
40
50
60
70

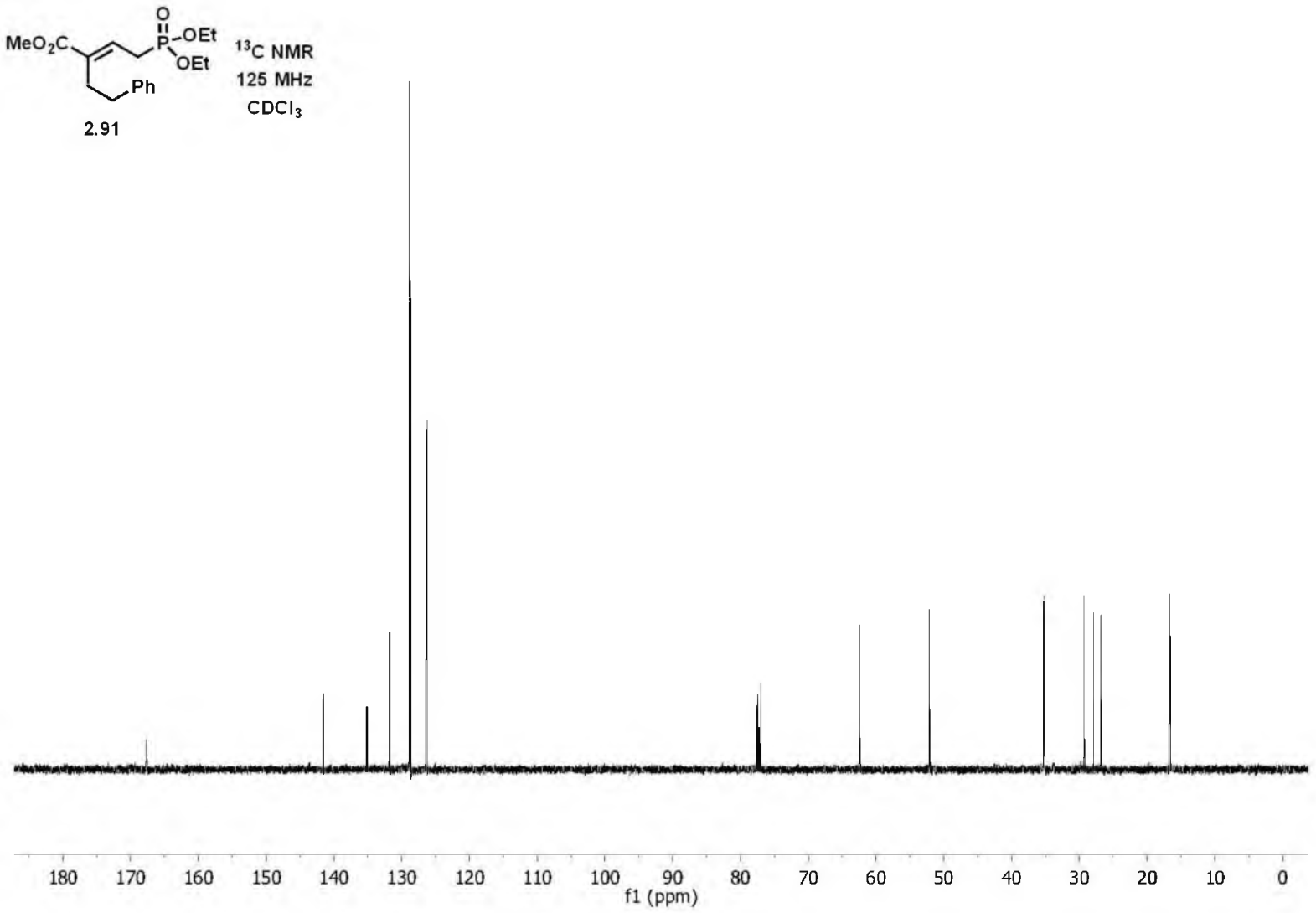


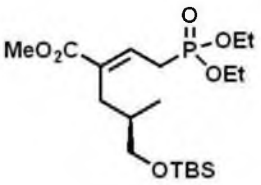
2.91

^{1}H NMR
300 MHz
$CDCl_3$



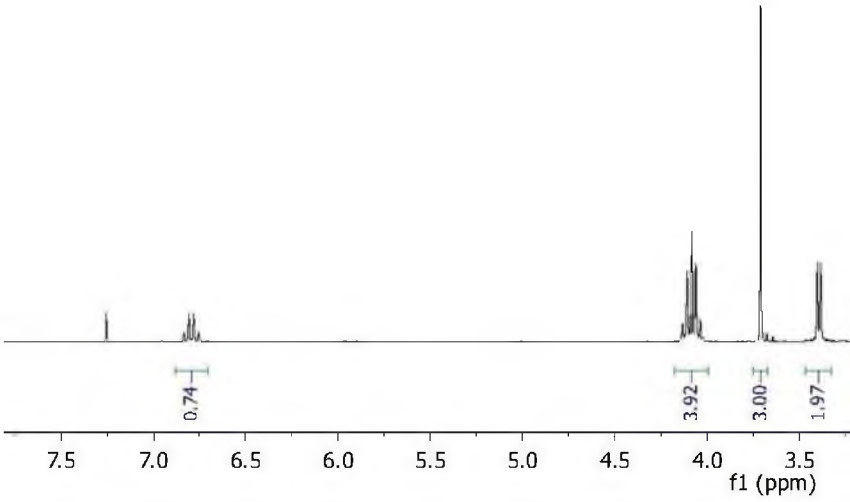

5.98
2.10
2.05
2.17
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0

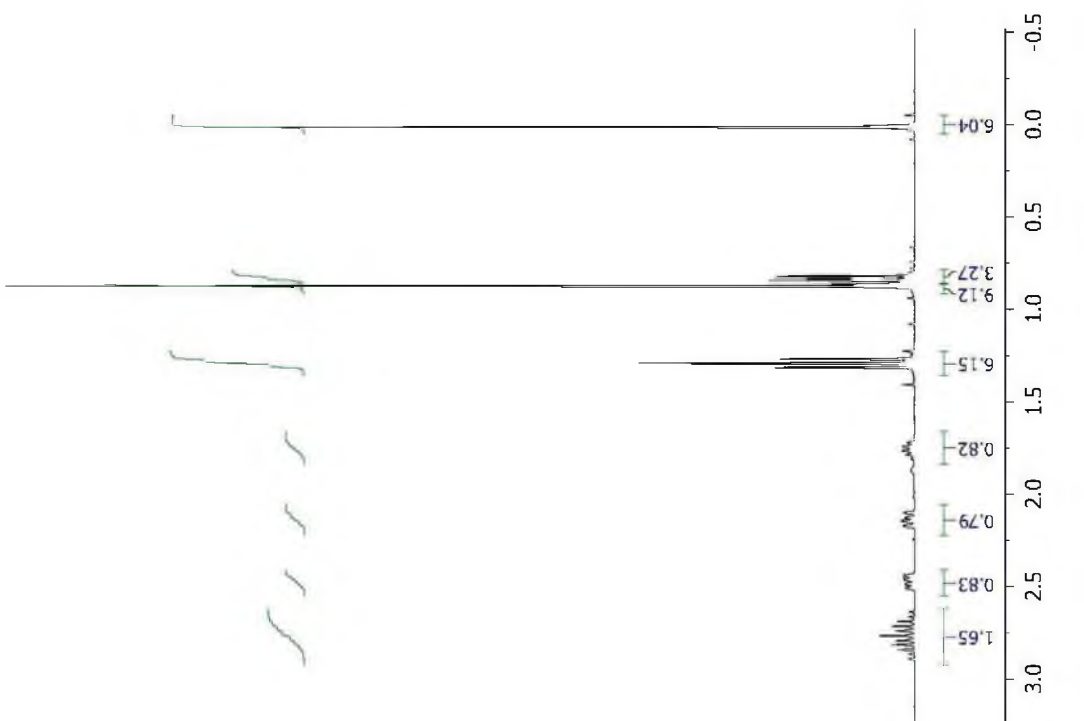

MeO2C
O
P
OEt
OEt
Ph
2.91
13C NMR
125 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

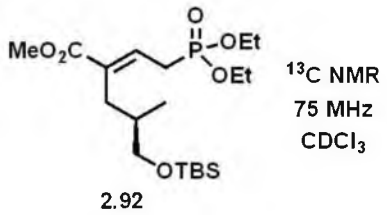


2.92

^{1}H NMR
300 MHz
$CDCl_3$

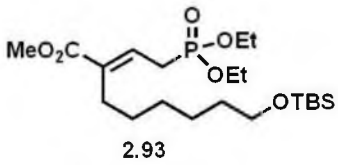



6.04
3.27
9.12
6.15
0.82
0.79
0.83
1.65
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5



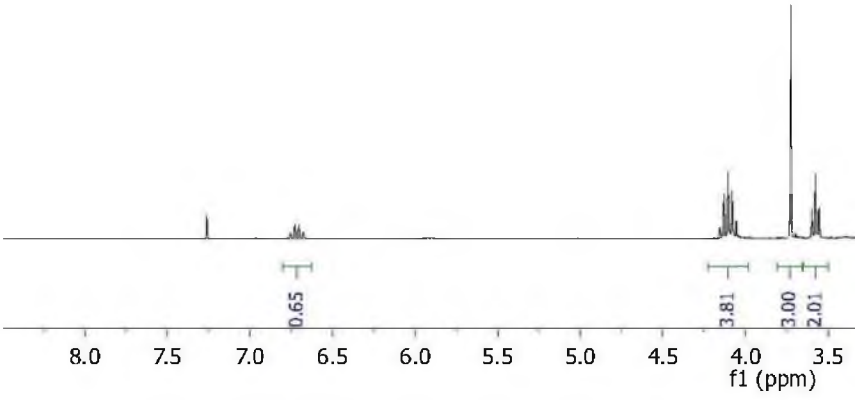
2.92

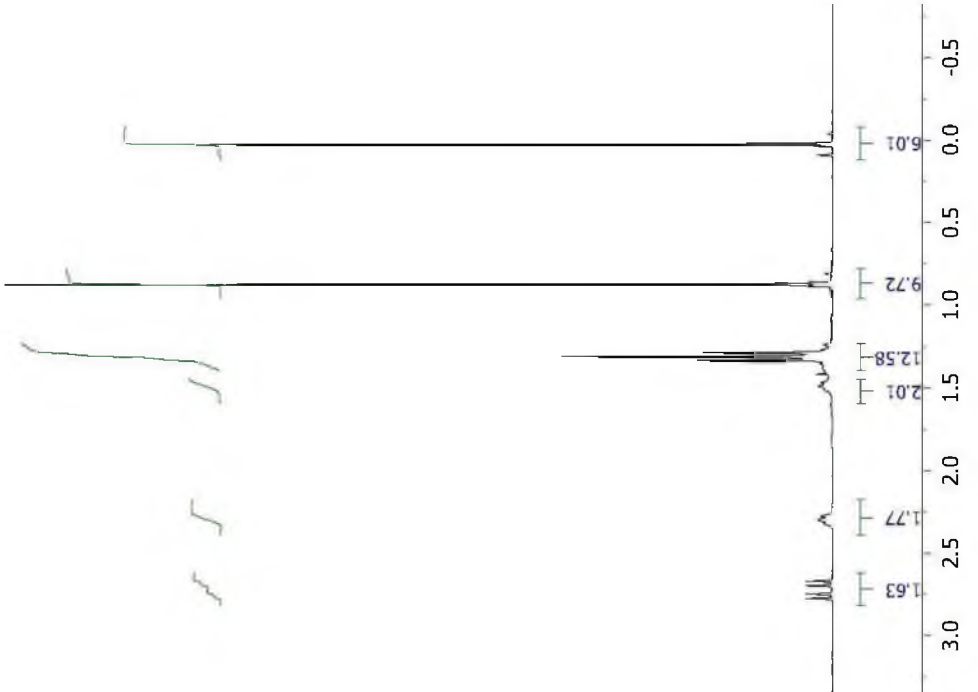
^{13}C NMR
75 MHz
$CDCl_3$

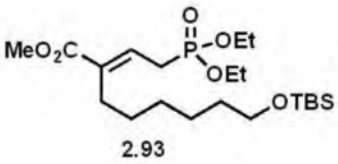


2.93

^{1}H NMR
300 MHz
$CDCl_3$

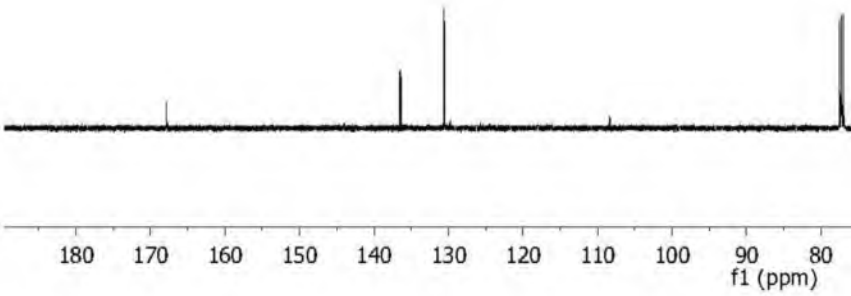


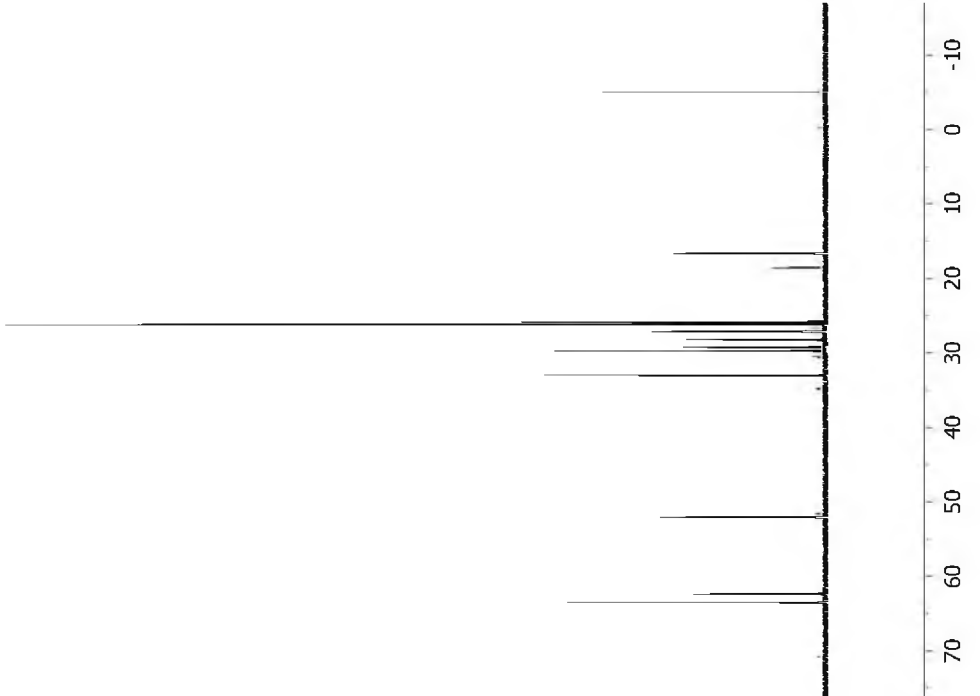

6.01
9.72
12.58
2.01
1.77
1.63
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

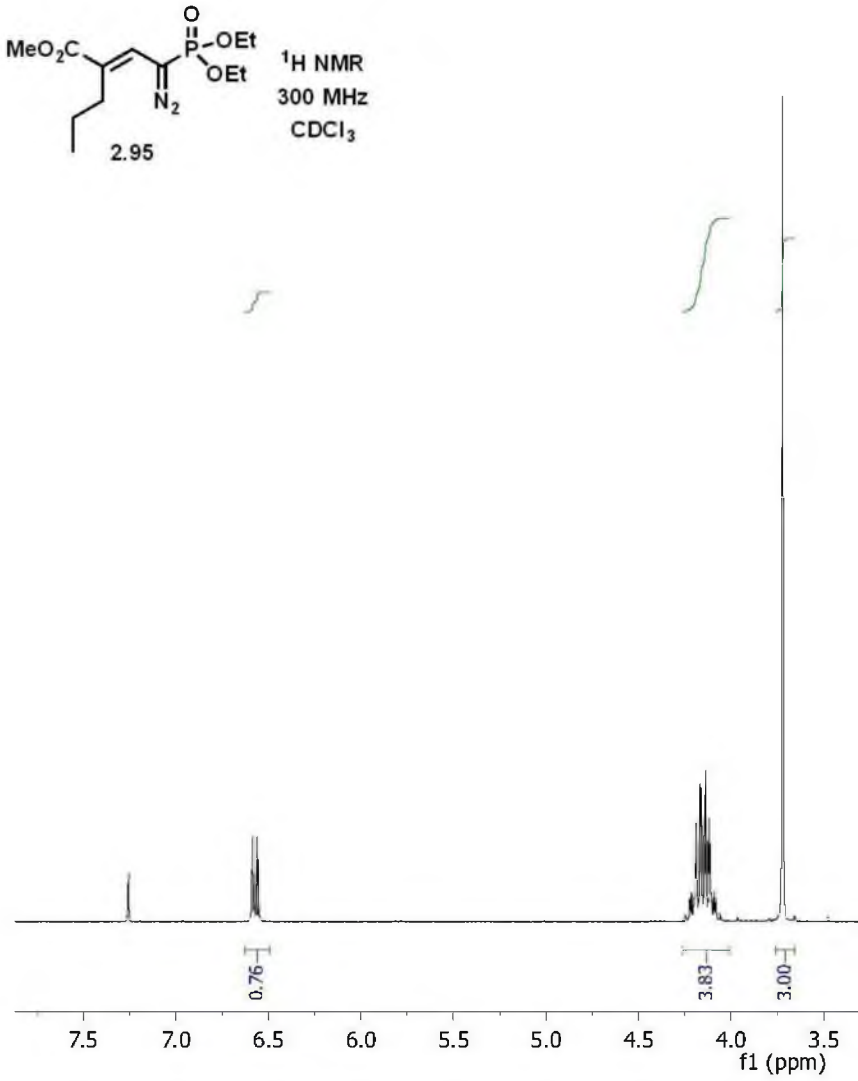


2.93

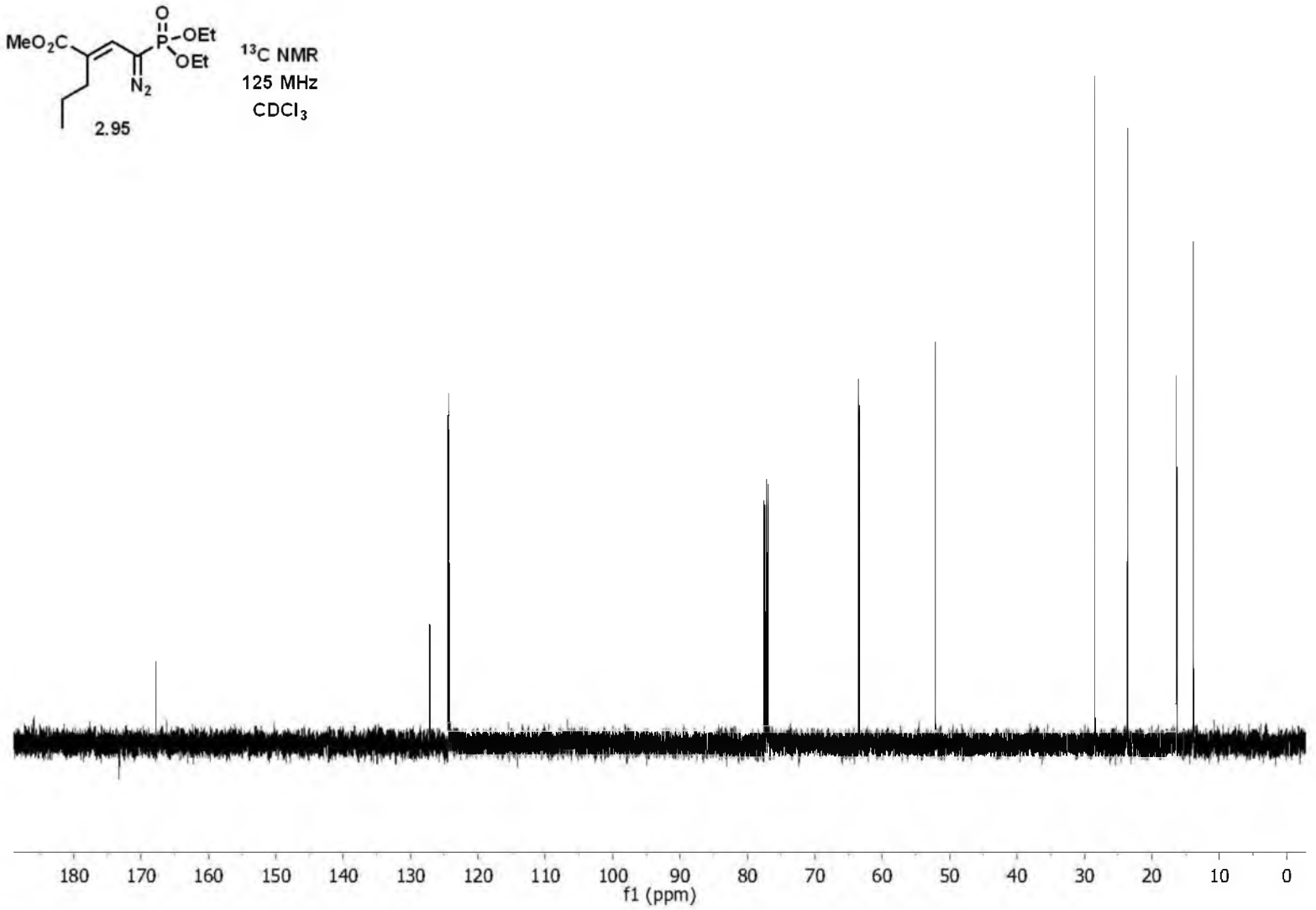
^{13}C NMR
125 MHz
$CDCl_3$

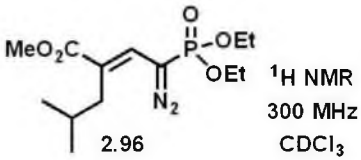



-10
0
10
20
30
40
50
60
70


MeO2C
O
P
OEt
OEt
N2
2.95
1H NMR
300 MHz
CDCl3
0.76
3.83
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

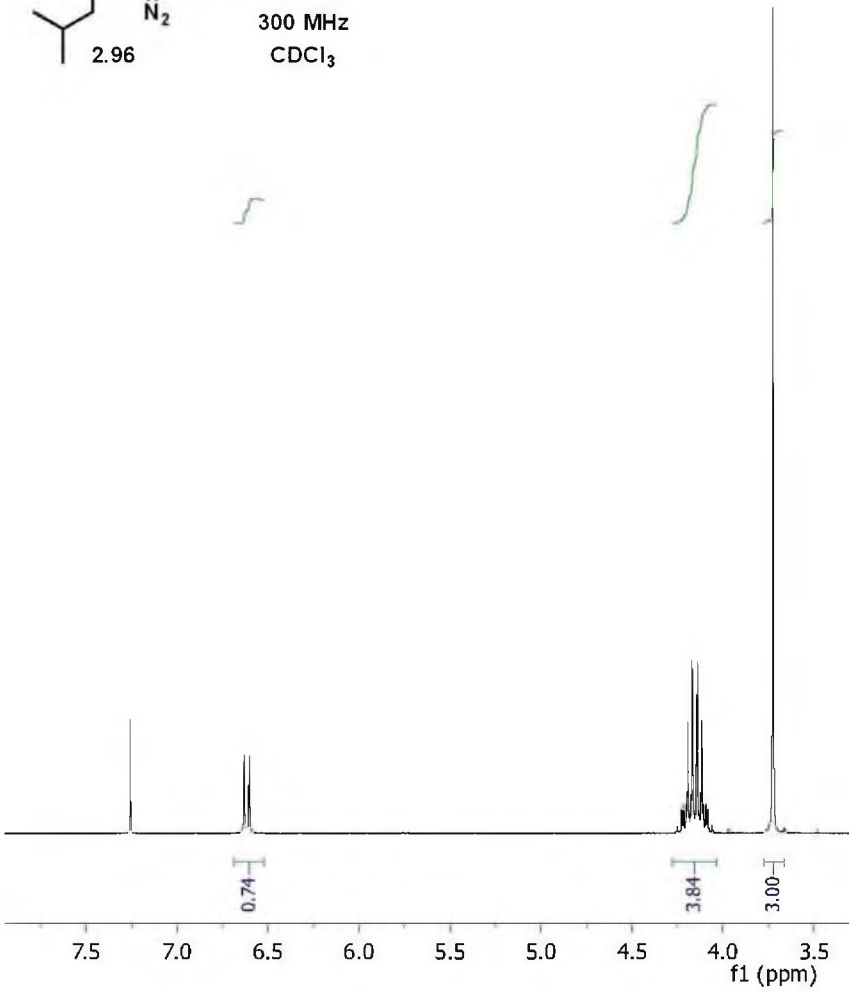
2.03
8.19
3.10
3.0
2.5
2.0
1.5
1.0
0.5
0.0

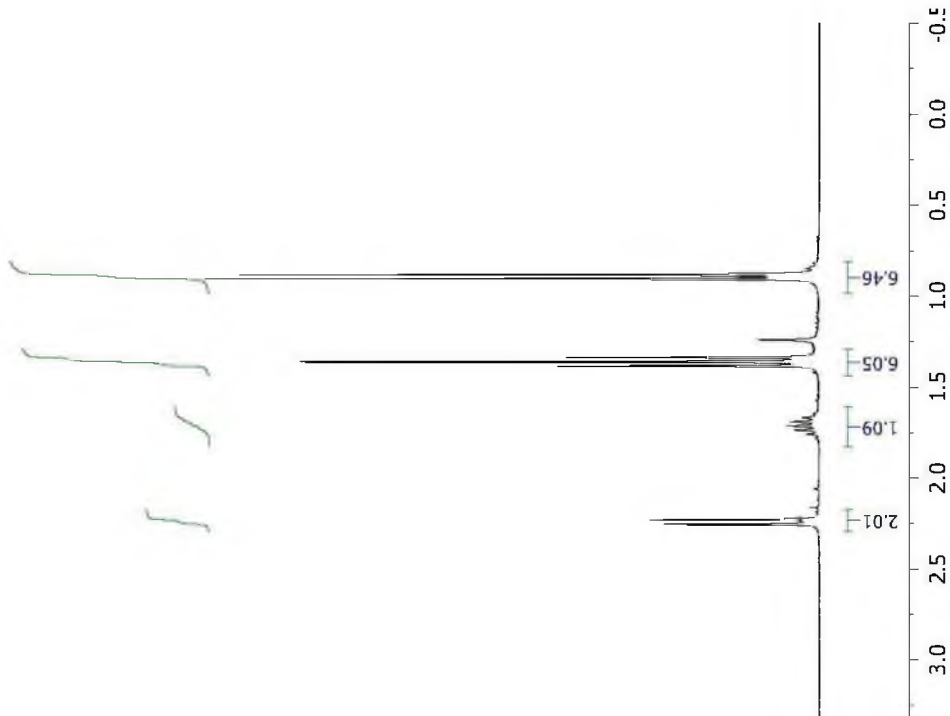

MeO2C
O
P
OEt
OEt
N2
2.95
13C NMR
125 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

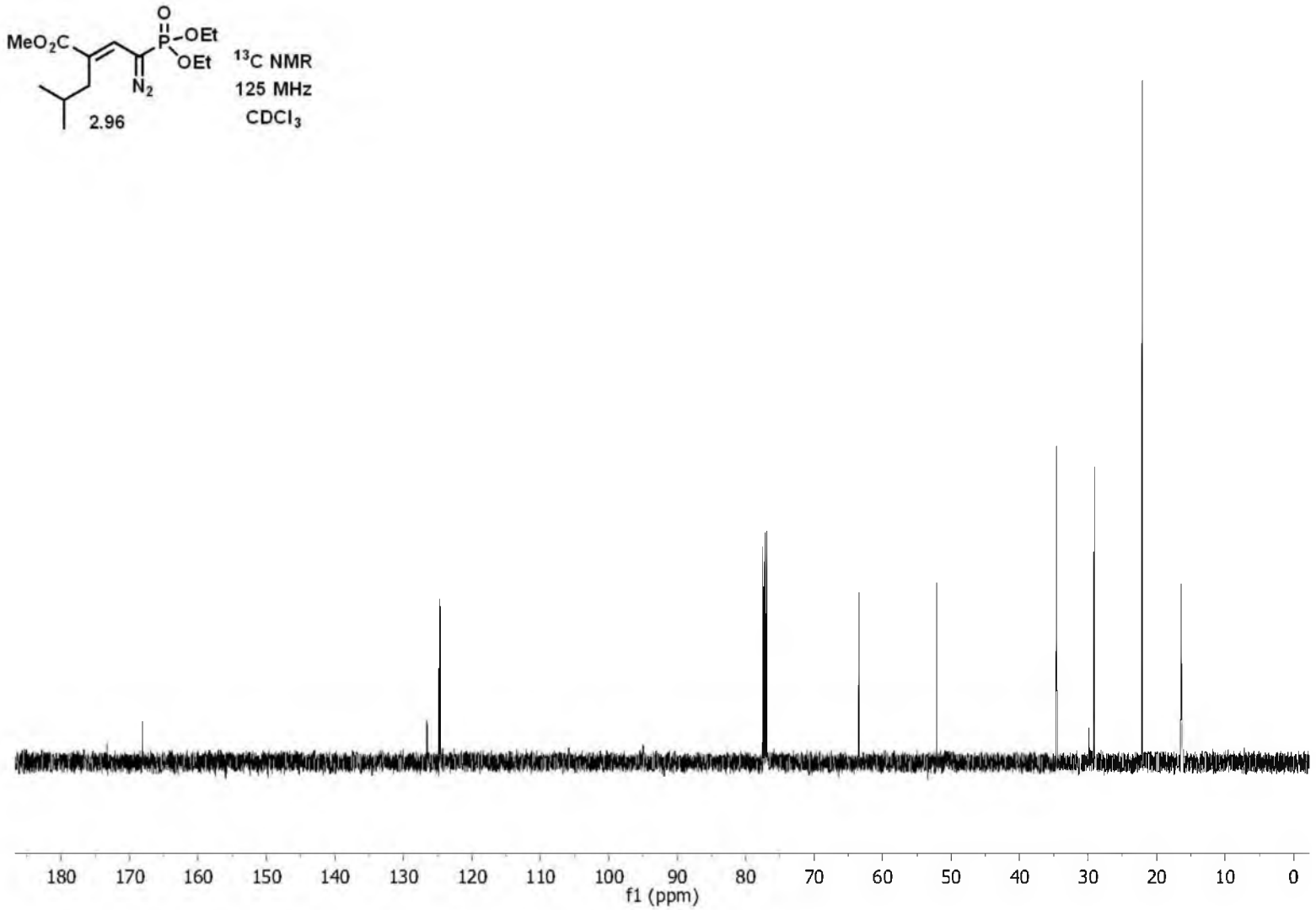


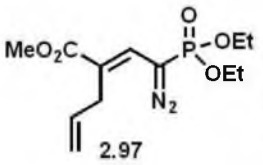
2.96

^{1}H NMR
300 MHz
$CDCl_3$

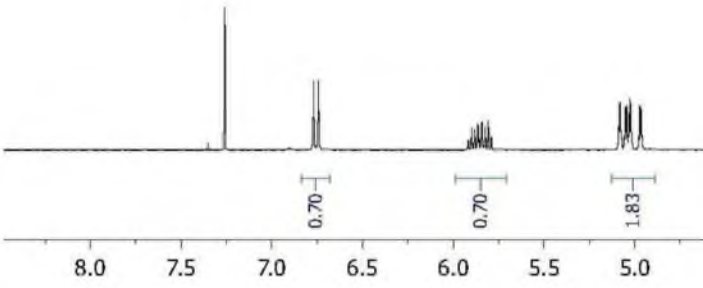


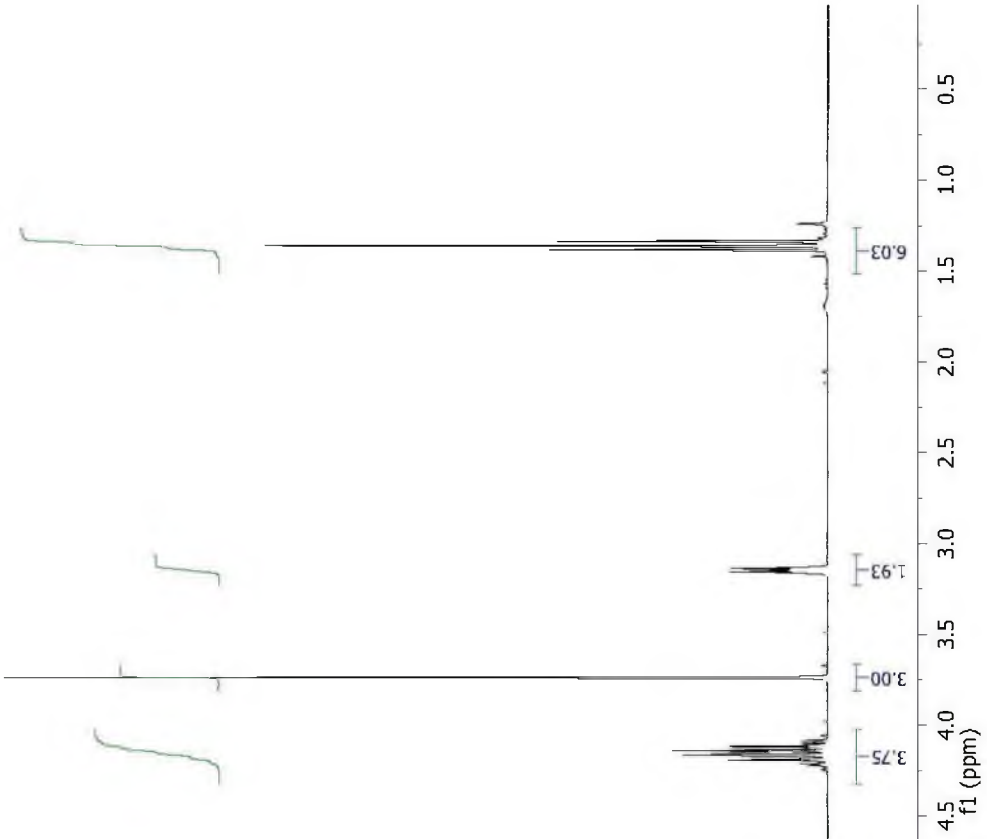

6.46
6.05
1.09
2.01
3.0
2.5
2.0
1.5
1.0
0.5
0.0

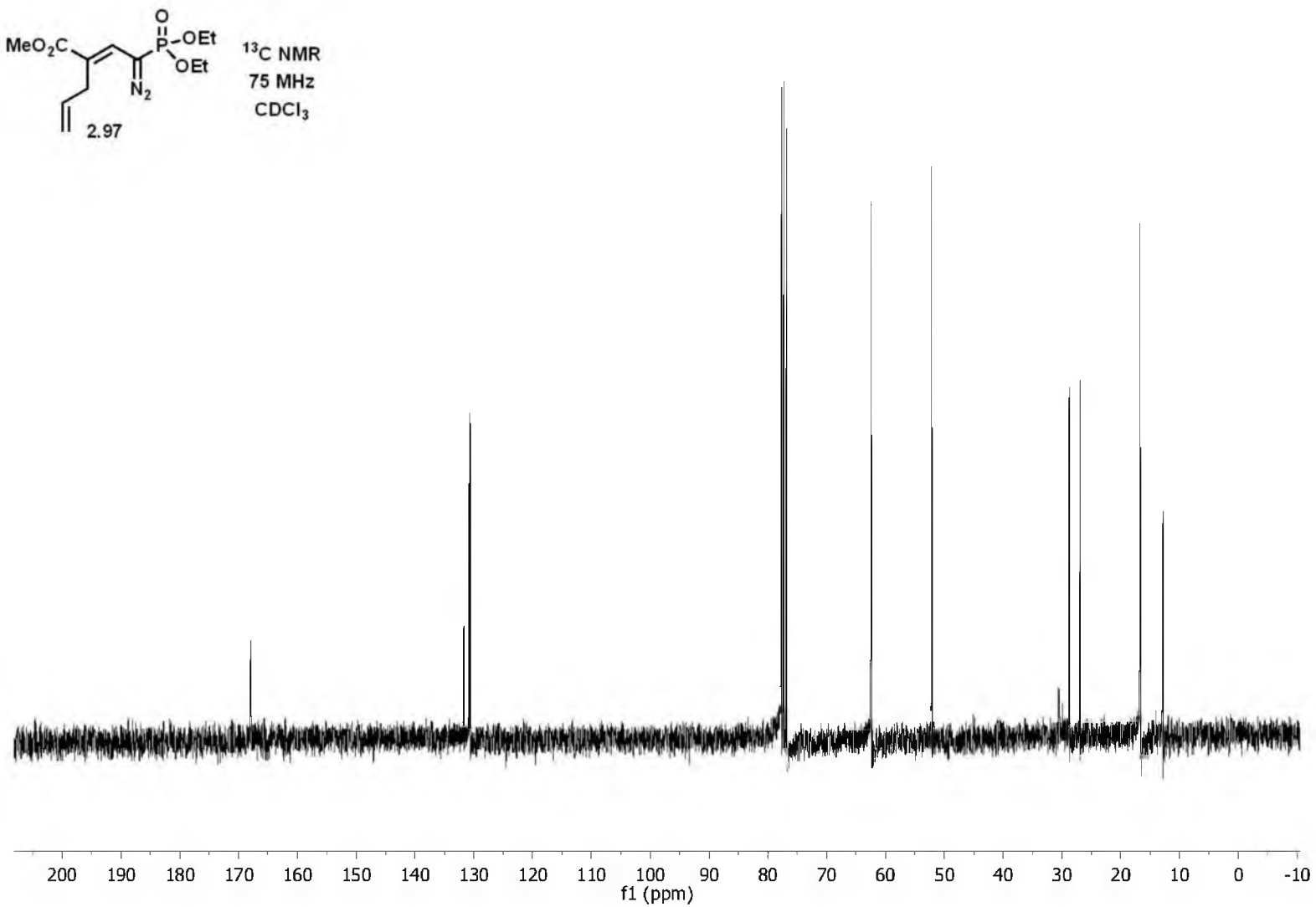

MeO2C
O
P
OEt
OEt
N2
2.96
13C NMR
125 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

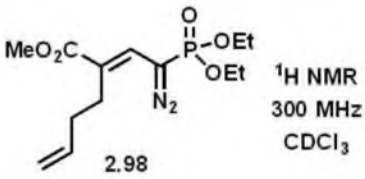


^{1}H NMR
300 MHz
$CDCl_3$



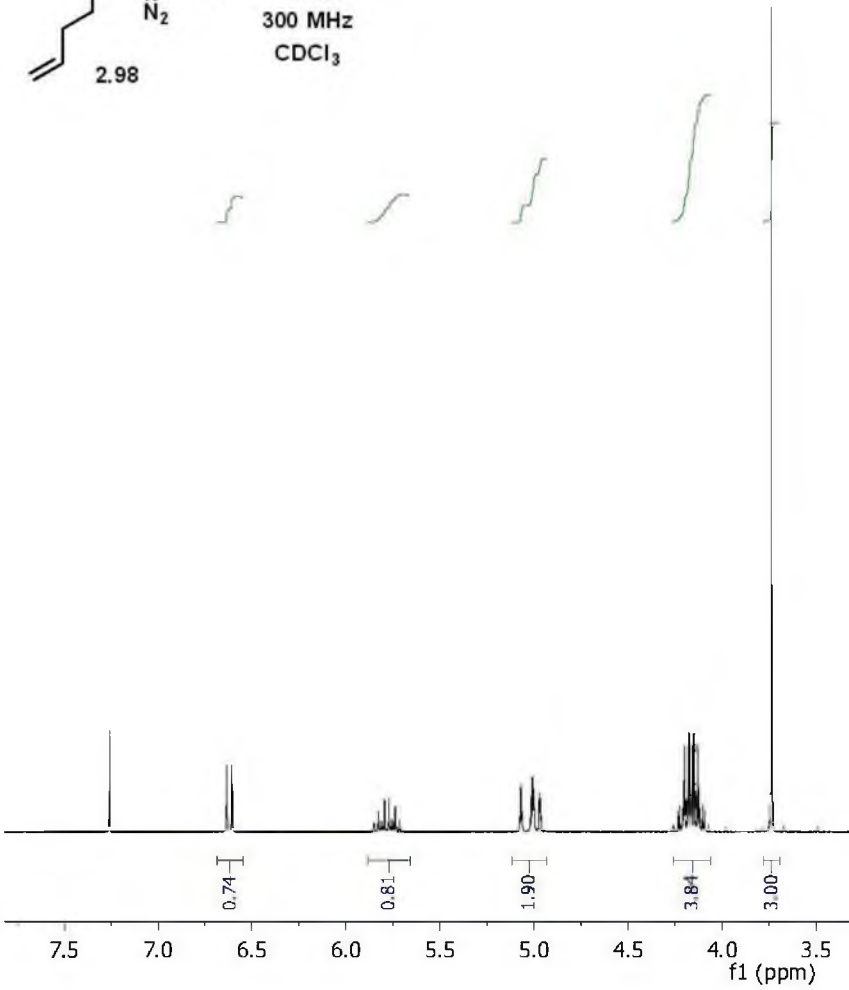

6.03
1.93
3.00
3.75
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


MeO2C
O
P
OEt
OEt
N2
2.97
13C NMR
75 MHz
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

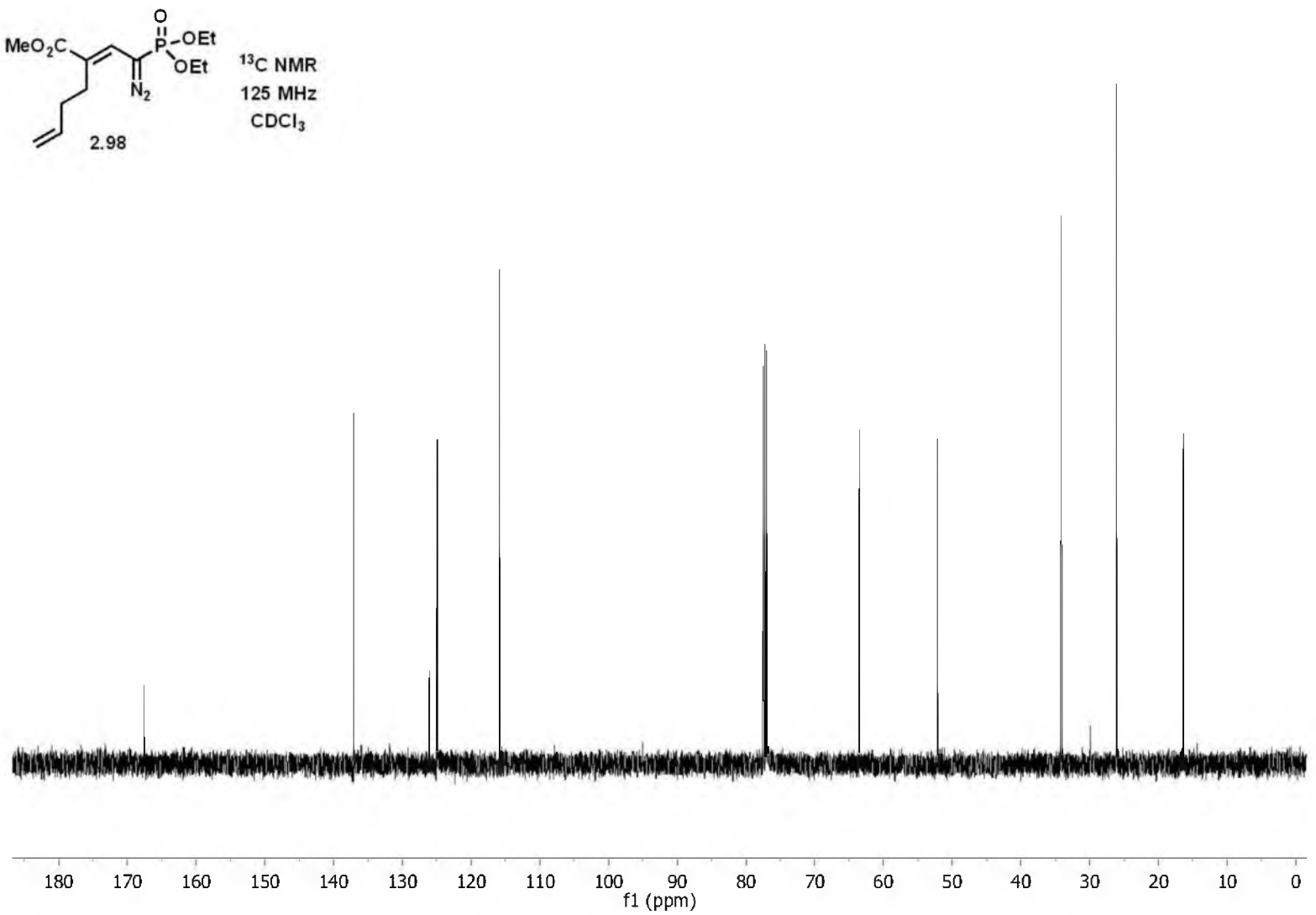


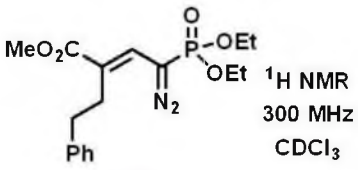
2.98

^{1}H NMR
300 MHz
$CDCl_3$



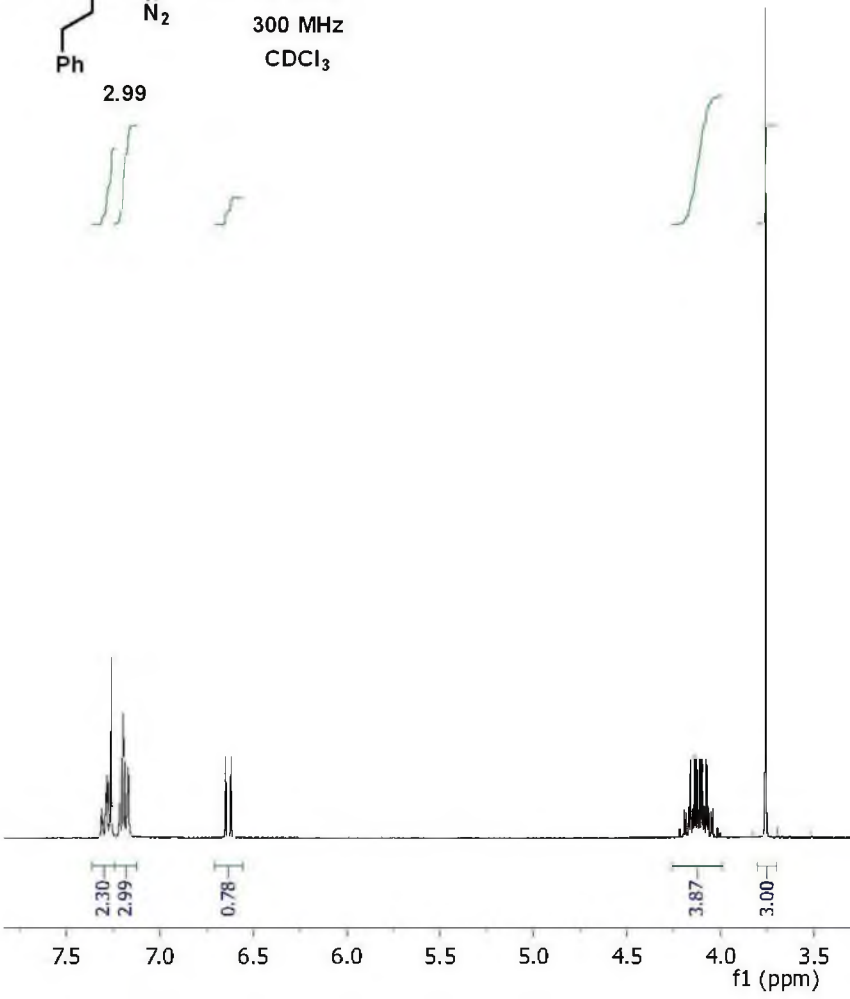
2.02
2.05
5.97
3.0
2.5
2.0
1.5
1.0
0.5
0.0

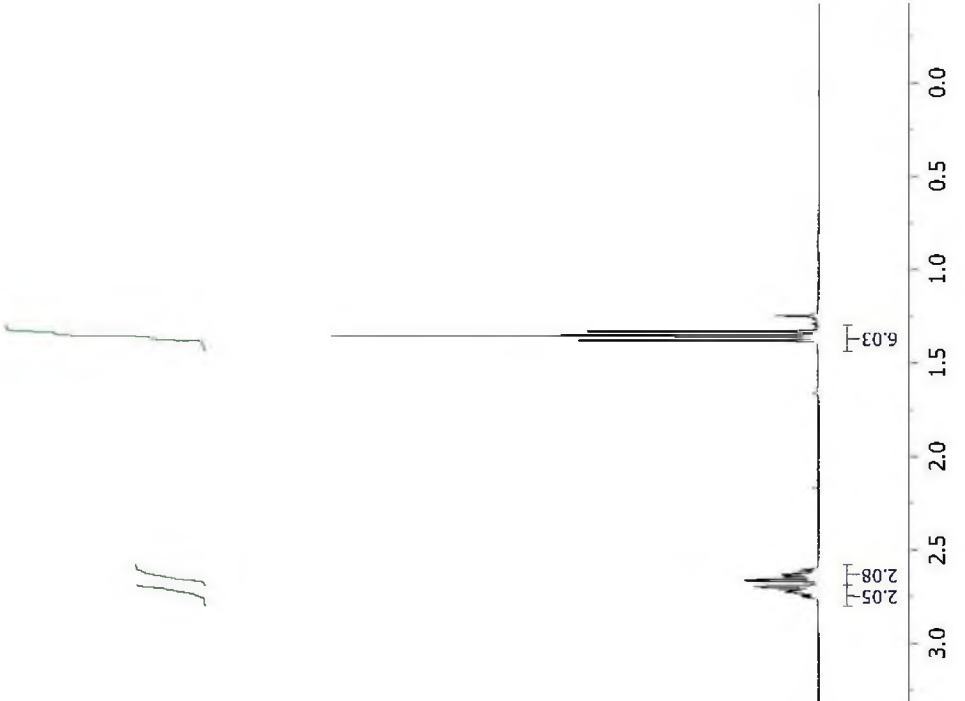

MeO2C
O
P
OEt
OEt
N2
2.98
13C NMR
125 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

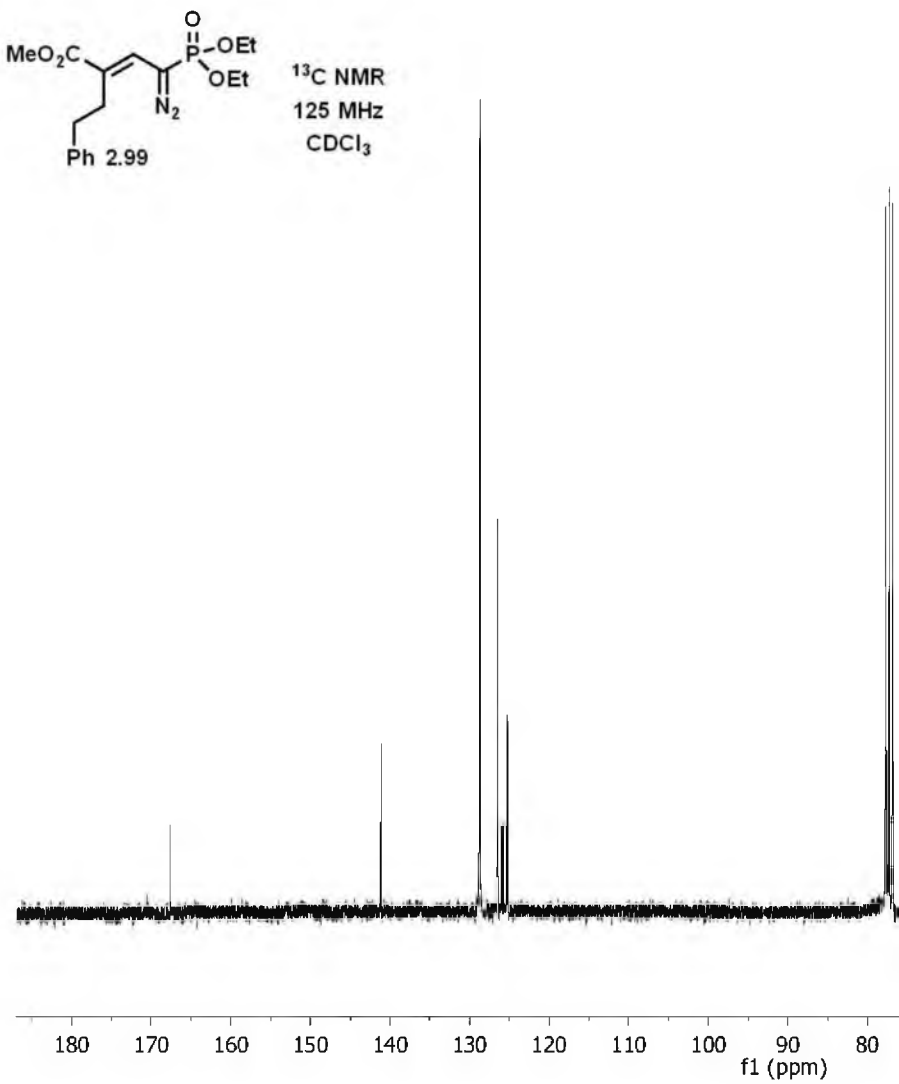


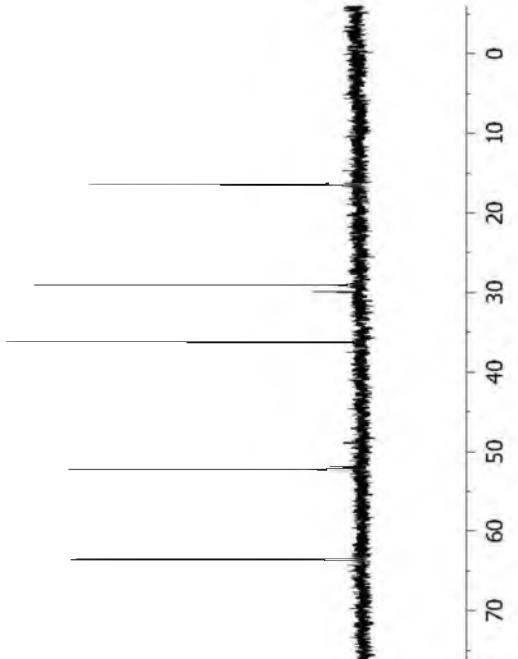
^{1}H NMR
300 MHz
$CDCl_3$

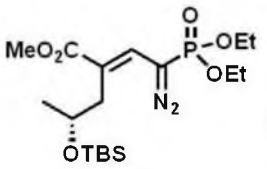
2.99




6.03
2.08
2.05
0.0
0.5
1.0
1.5
2.0
2.5
3.0

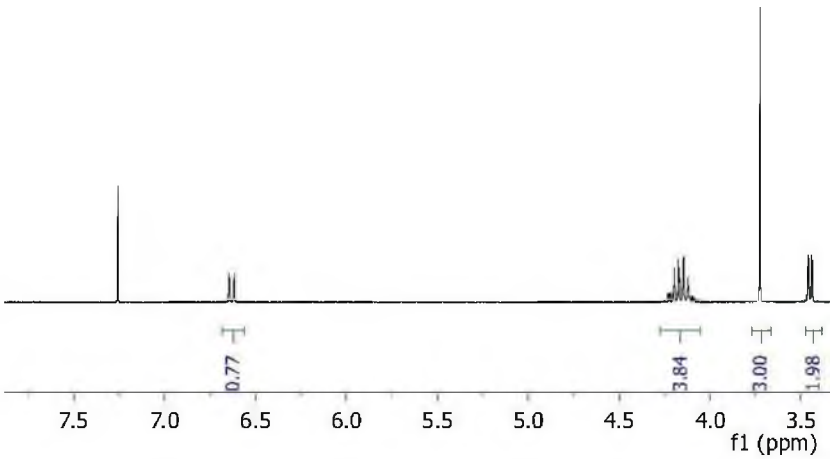

MeO2C
O
P
OEt
OEt
N2
Ph 2.99
13C NMR
125 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
f1 (ppm)

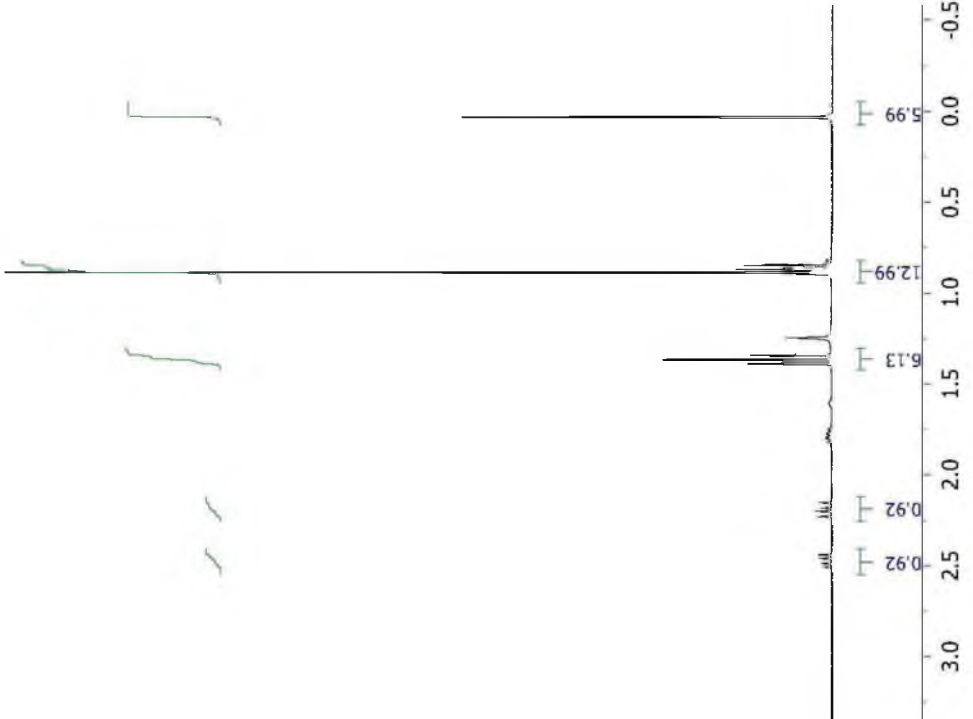

0
10
20
30
40
50
60
70

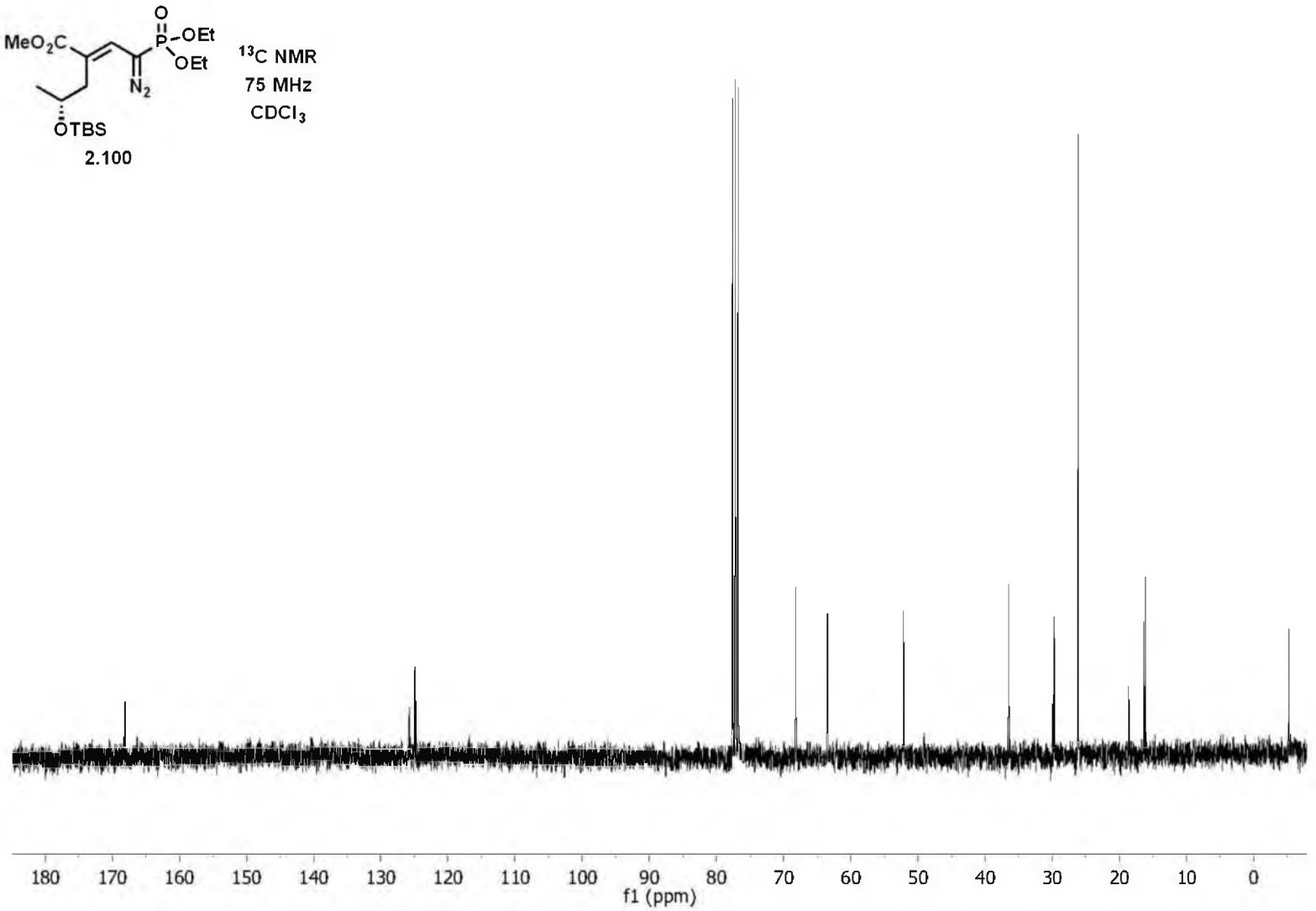


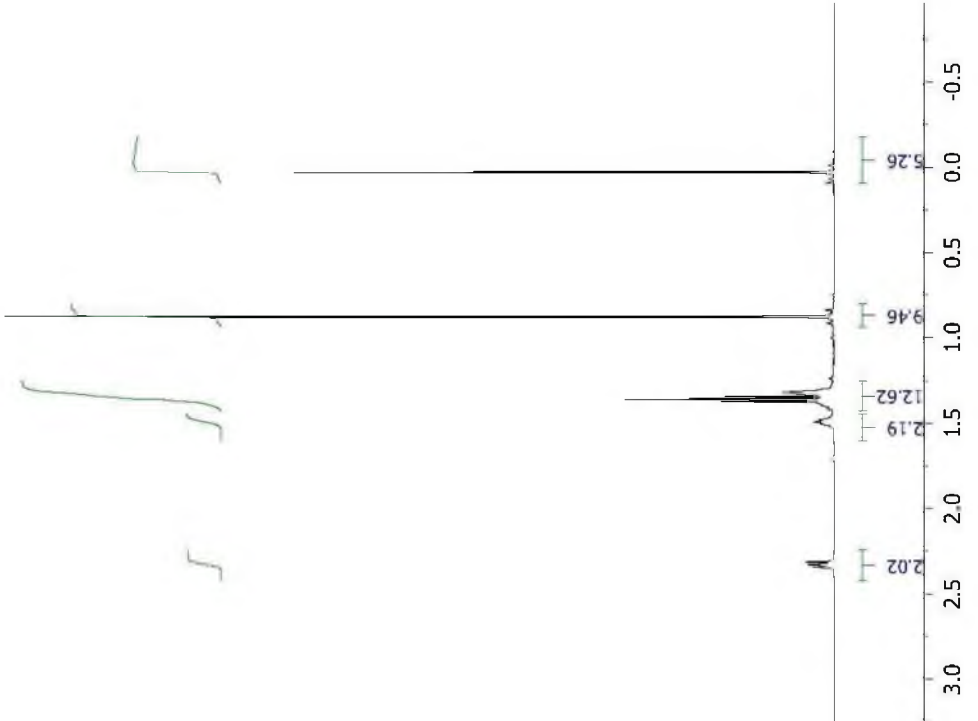
2.100

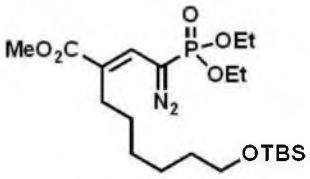
^{1}H NMR
300 MHz
$CDCl_3$




5.99
12.99
6.13
0.92
0.92
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0

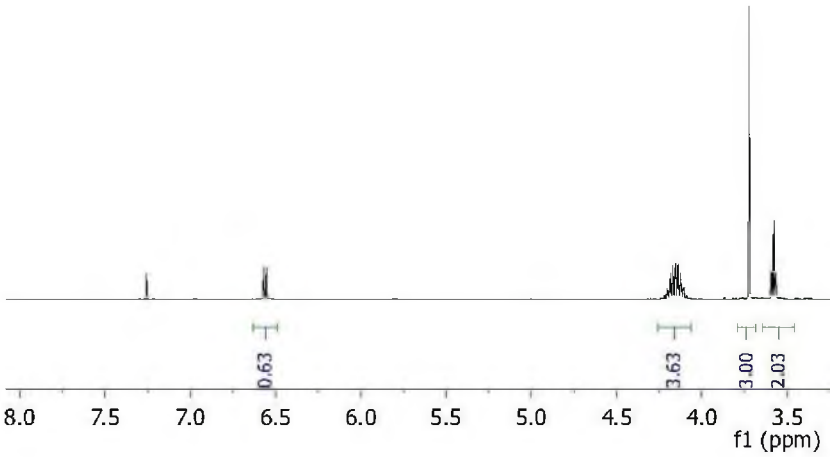

MeO2C
O
P
OEt
OEt
N2
OTBS
2.100
13C NMR
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

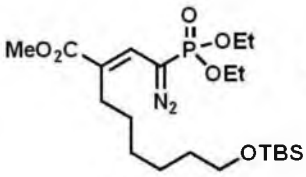

5.26
9.46
12.62
2.19
2.02
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0



2.101

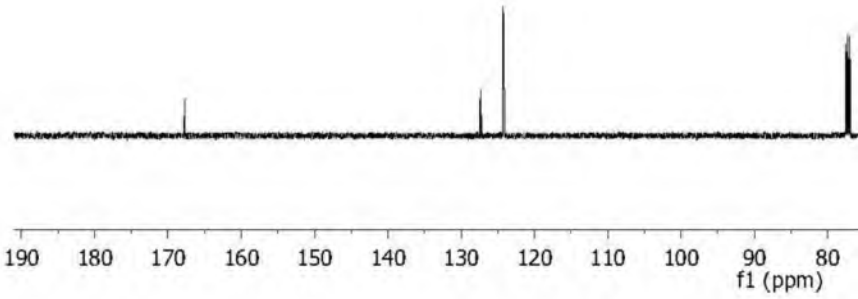
^{1}H NMR
500 MHz
$CDCl_3$

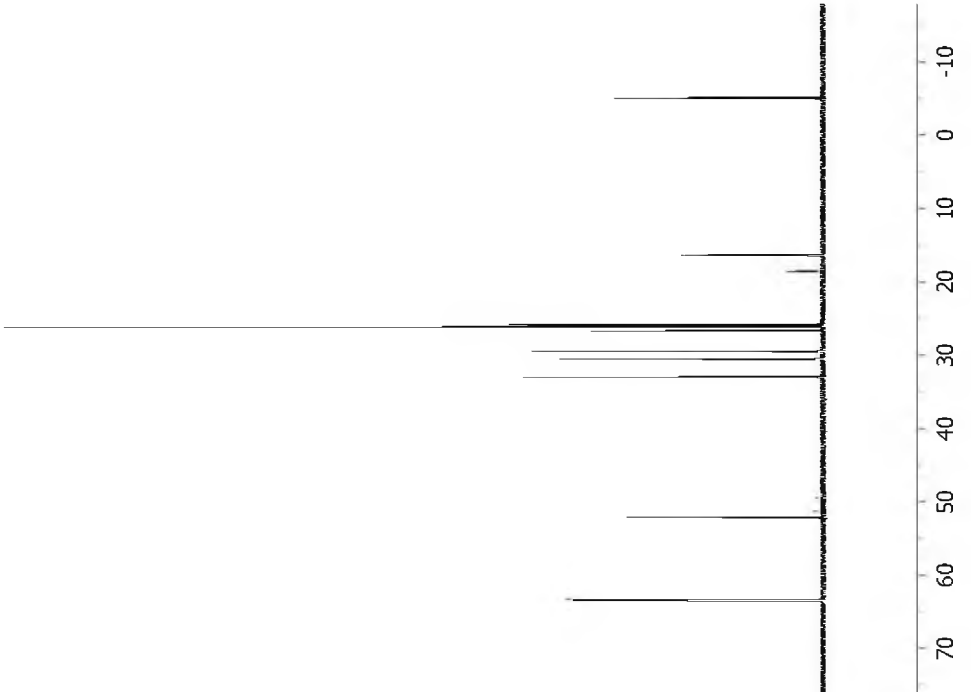


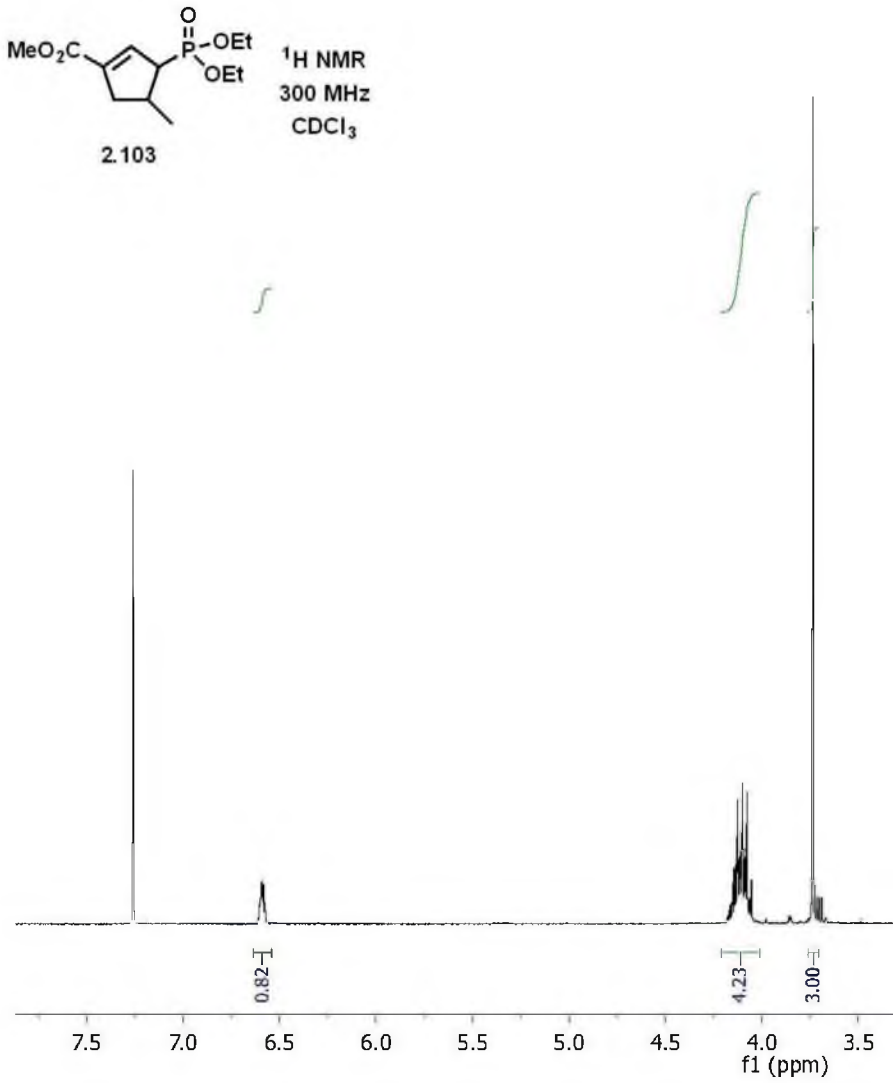


2.101

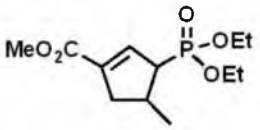
^{13}C NMR
125 MHz
$CDCl_3$




-10
0
10
20
30
40
50
60
70

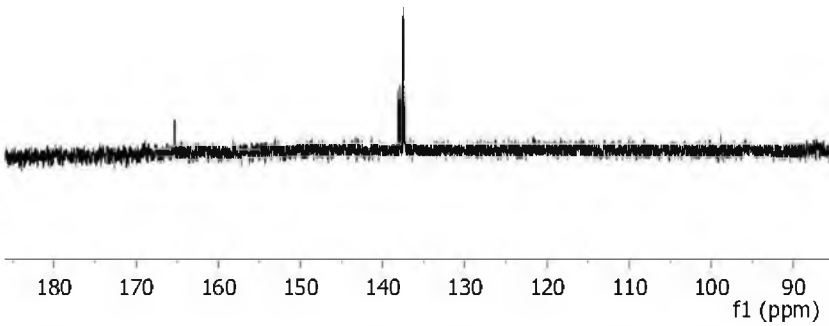

MeO2C
O
P
OEt
OEt
2.103
1H NMR
300 MHz
CDCl3
0.82
4.23
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

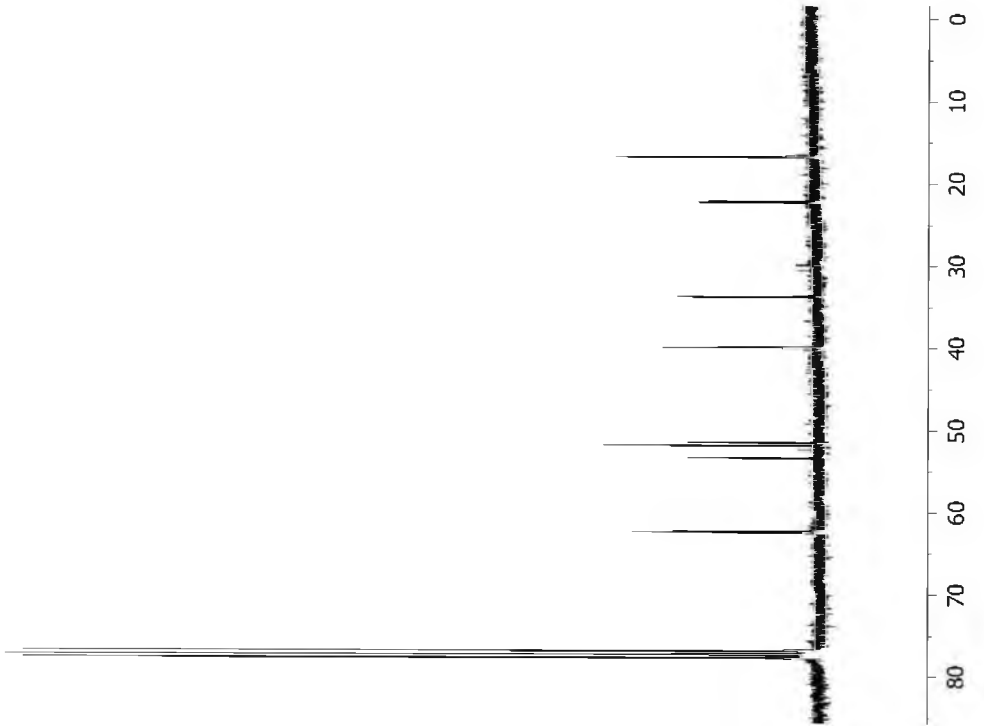
0.95
1.35
1.00
7.05
3.73
3.0
2.5
2.0
1.5
1.0
0.5
0.0

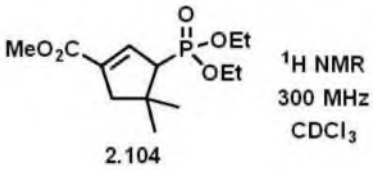


2.103

^{13}C NMR
75 MHz
$CDCl_3$

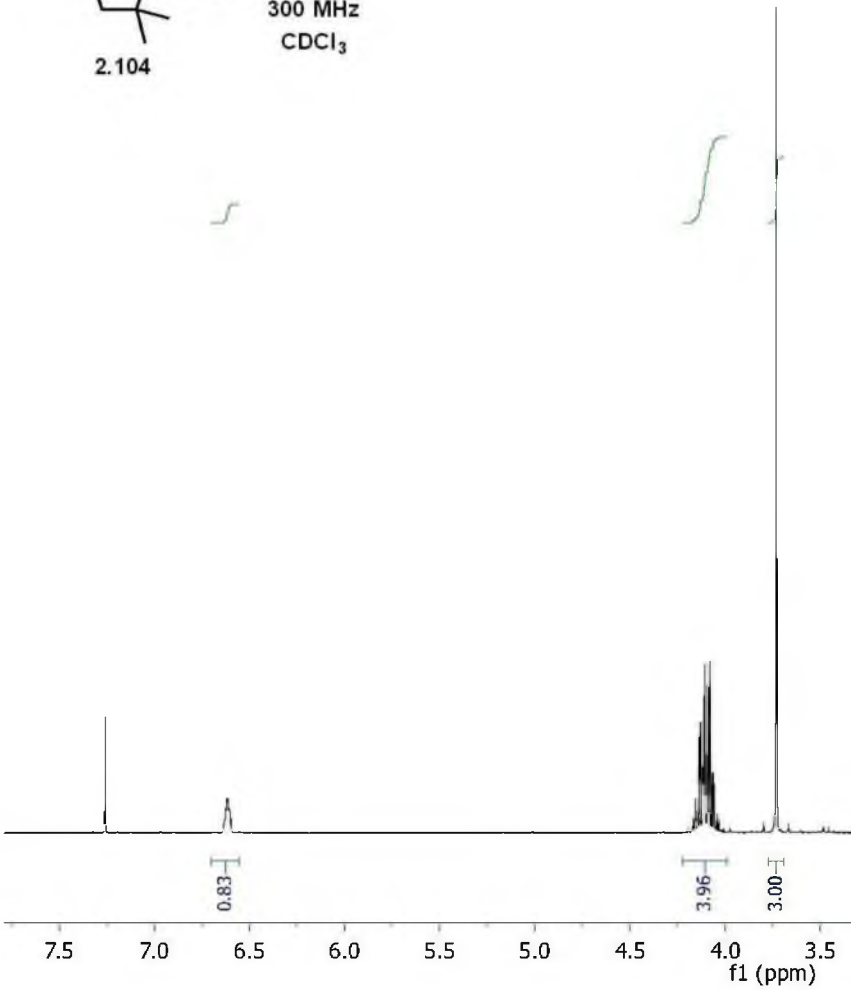



0
10
20
30
40
50
60
70
80

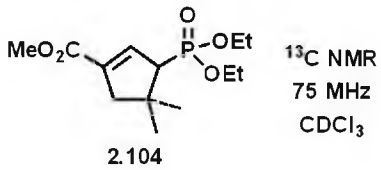


2.104

^{1}H NMR
300 MHz
$CDCl_3$

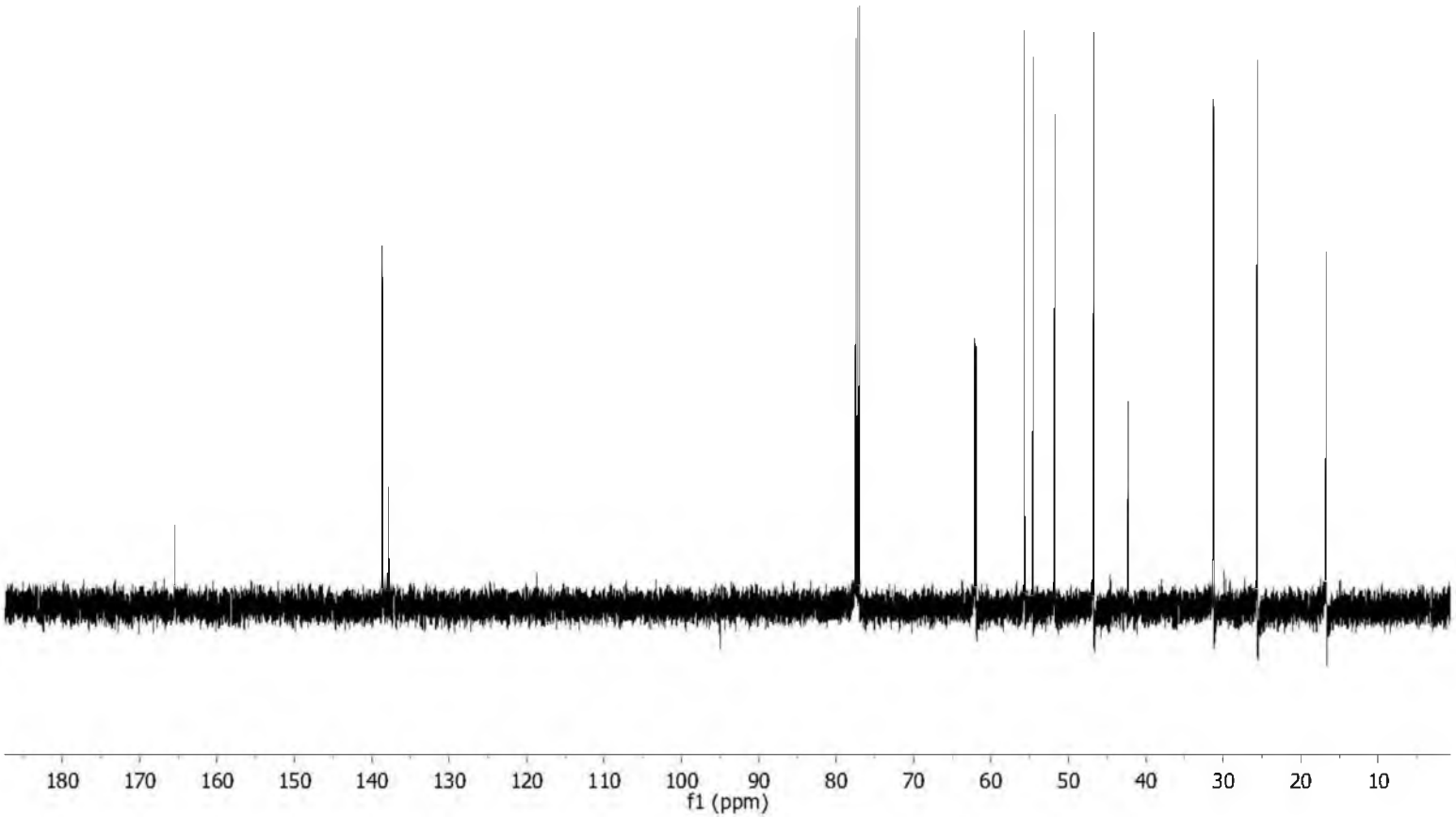


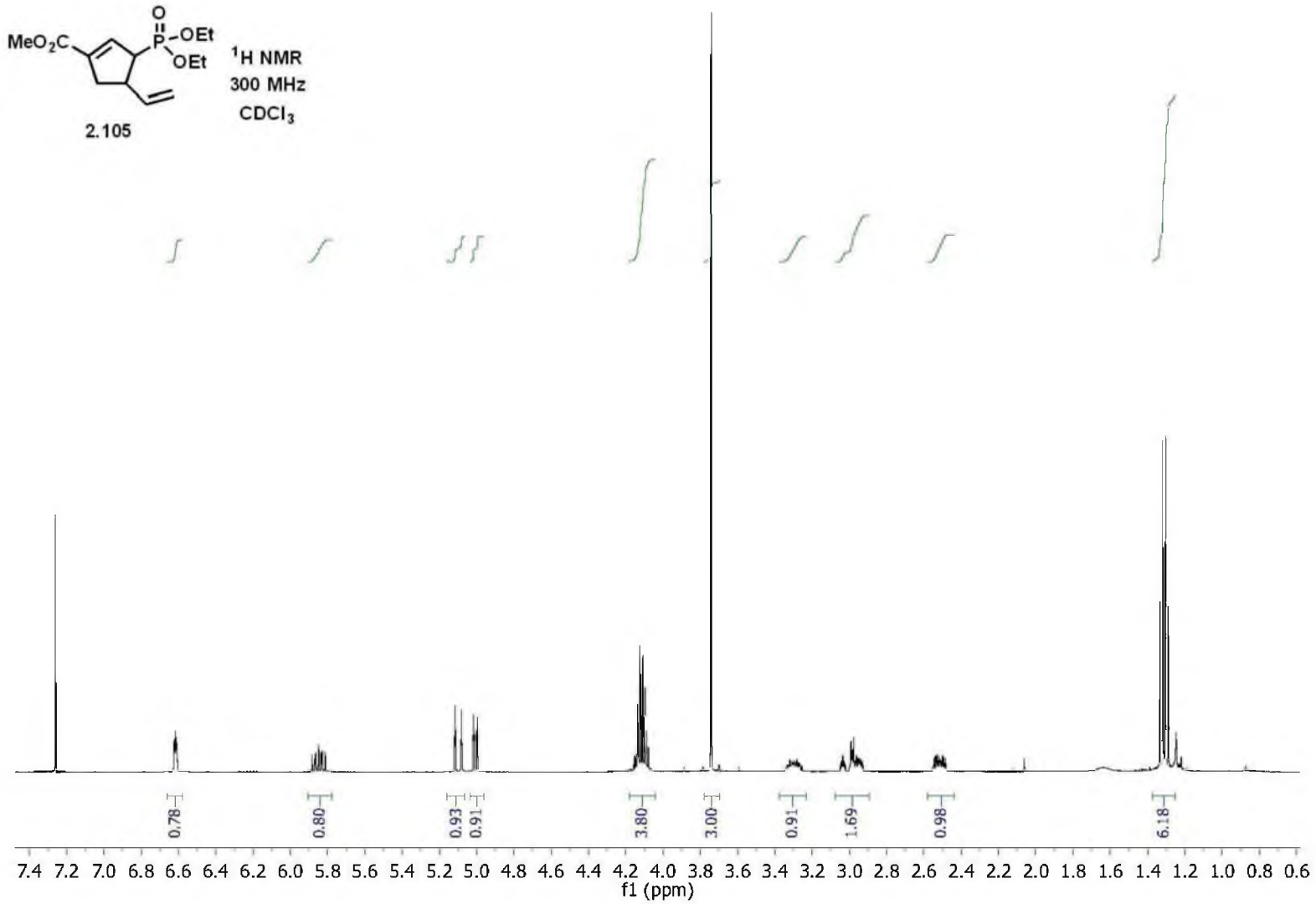
0.92
0.97
0.98
9.22
3.32
3.0
2.5
2.0
1.5
1.0
0.5
0.0

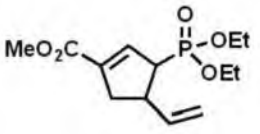


2.104

^{13}C NMR
75 MHz
$CDCl_3$

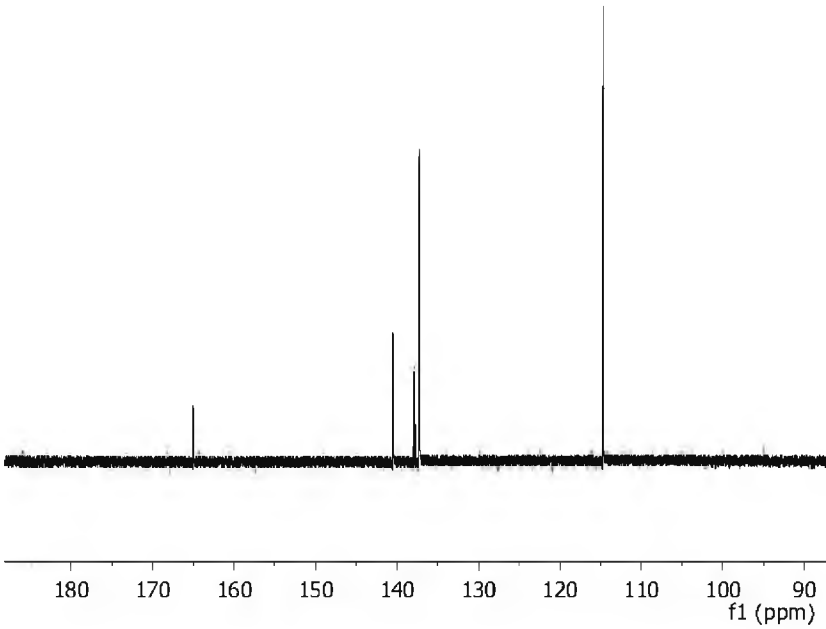


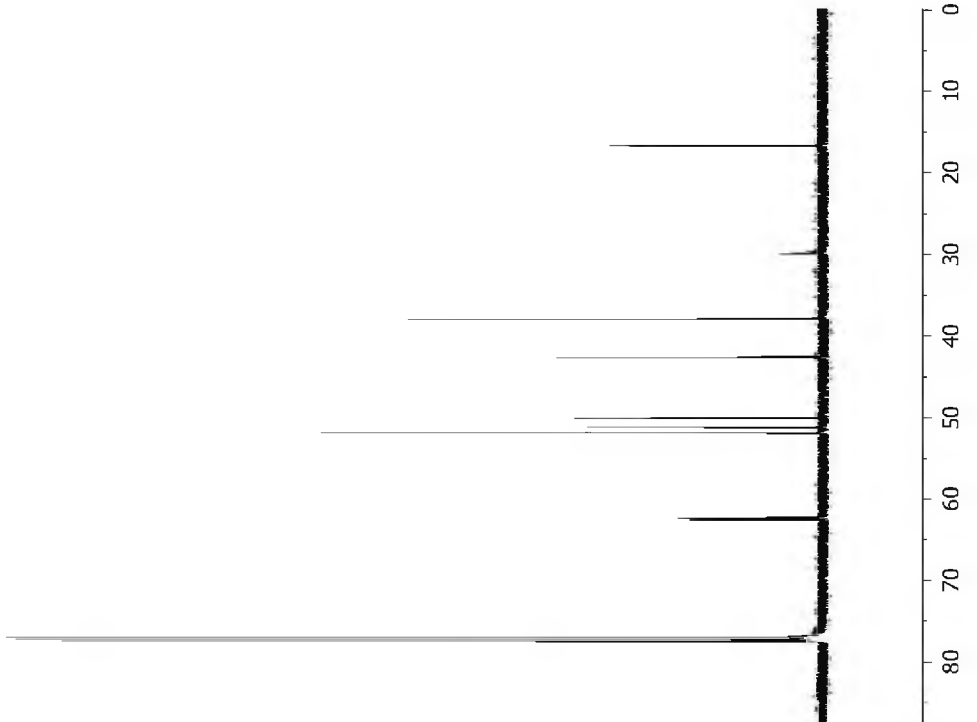

MeO2C
O
P
OEt
OEt
2.105
1H NMR
300 MHz
CDCl3
0.78
0.80
0.93
0.91
3.80
3.00
0.91
1.69
0.98
6.18
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

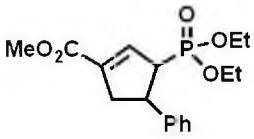


2.105

^{13}C NMR
125 MHz
$CDCl_3$

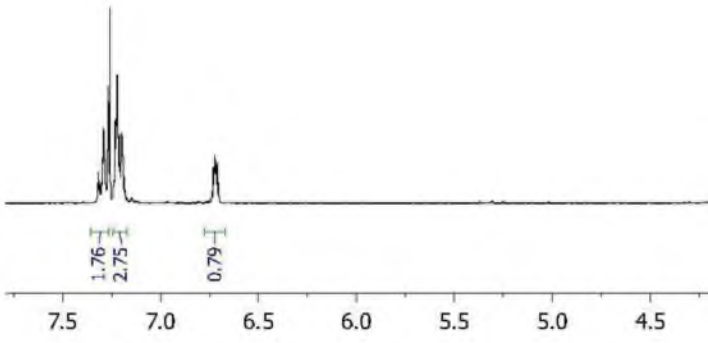


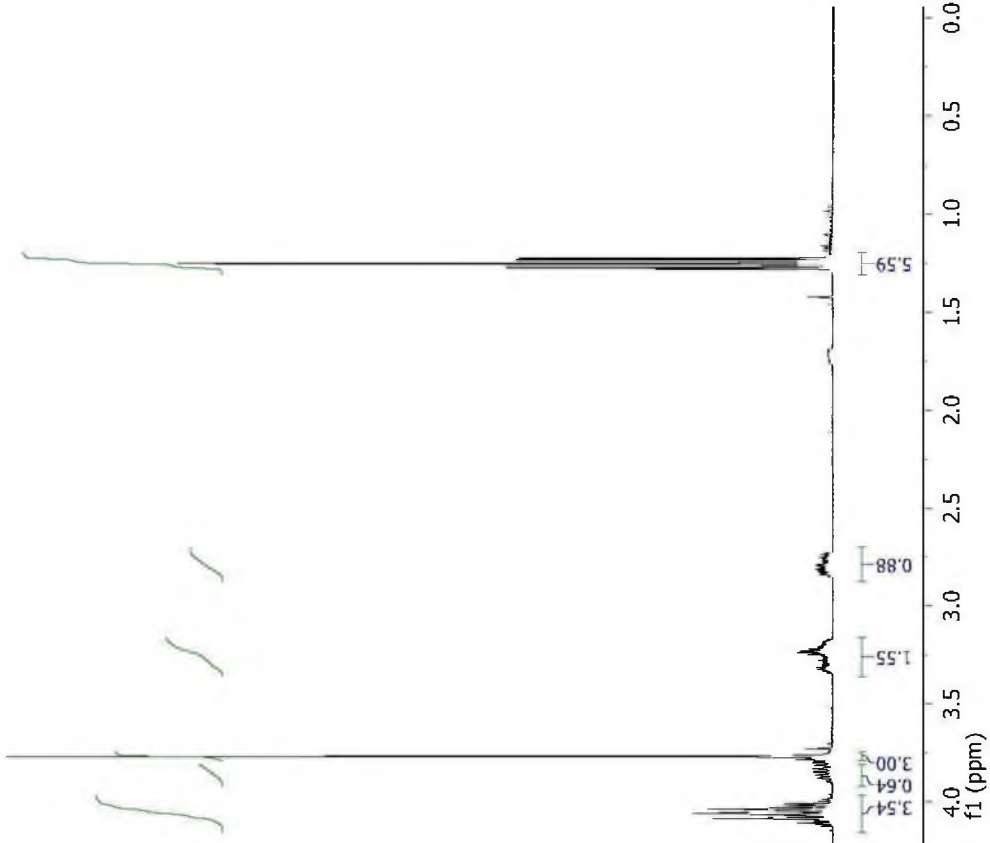

0
10
20
30
40
50
60
70
80

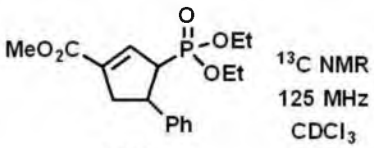


^{1}H NMR
300 MHz
$CDCl_3$

2.106

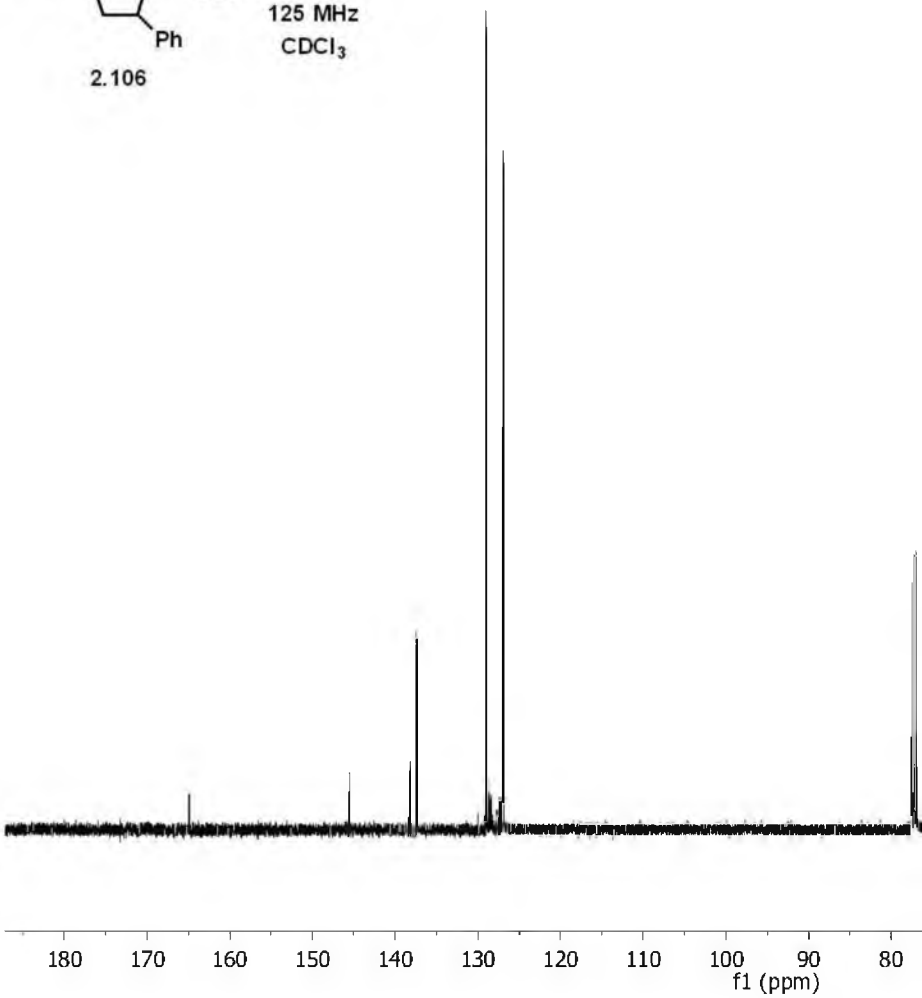


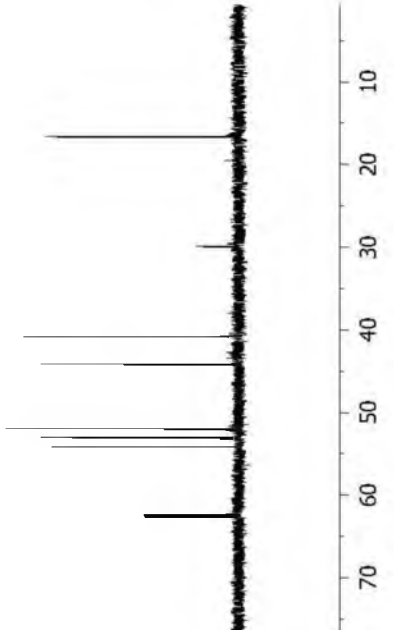

5.59
0.88
1.55
3.00
0.64
3.54
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

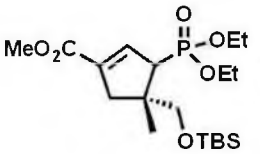


2.106

^{13}C NMR
125 MHz
$CDCl_3$

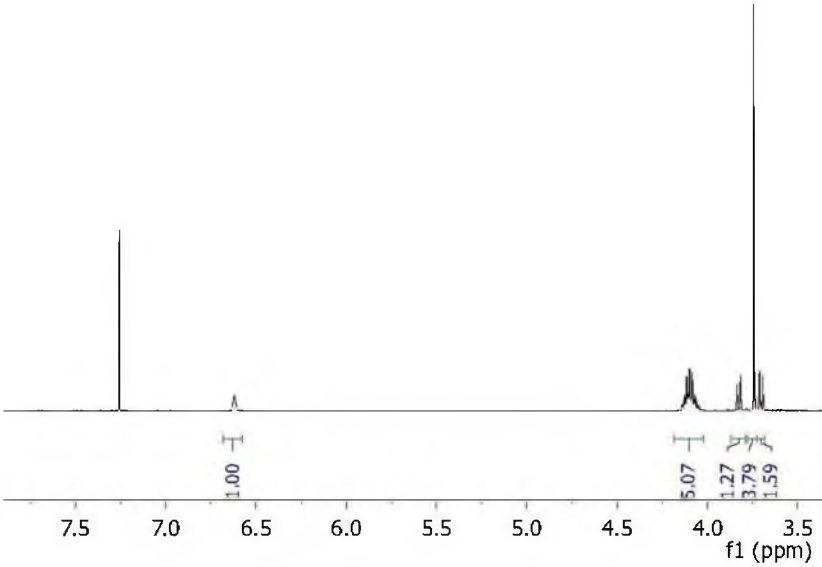


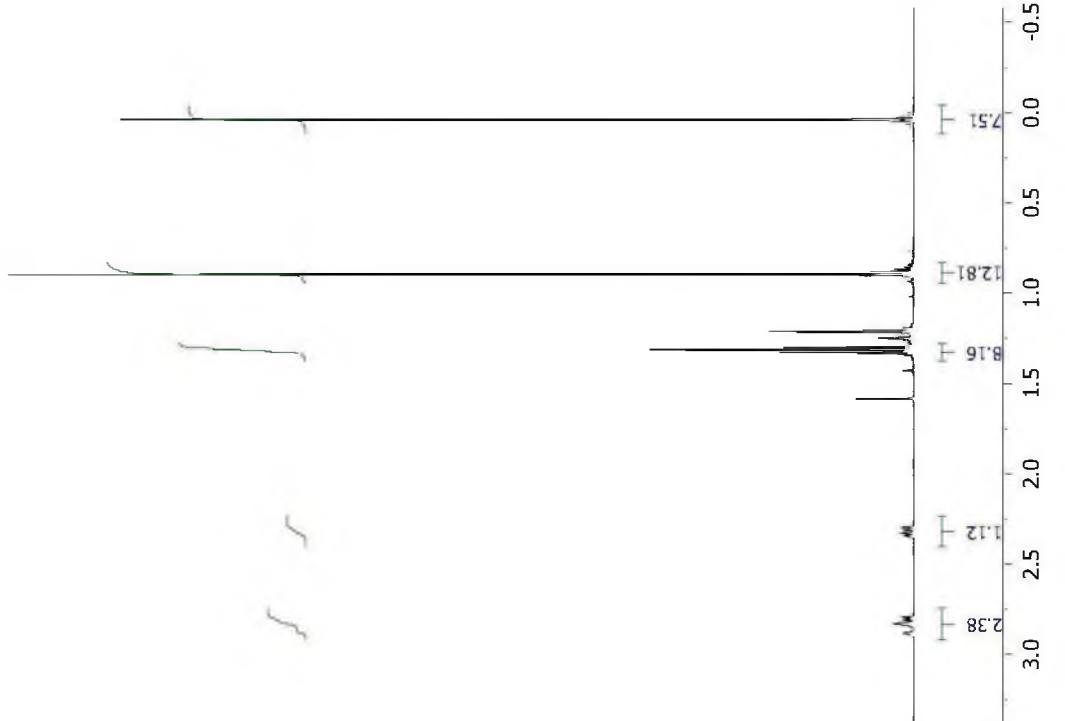

10
20
30
40
50
60
70

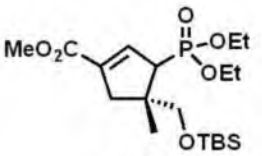


2.107

^{1}H NMR
500 MHz
$CDCl_3$

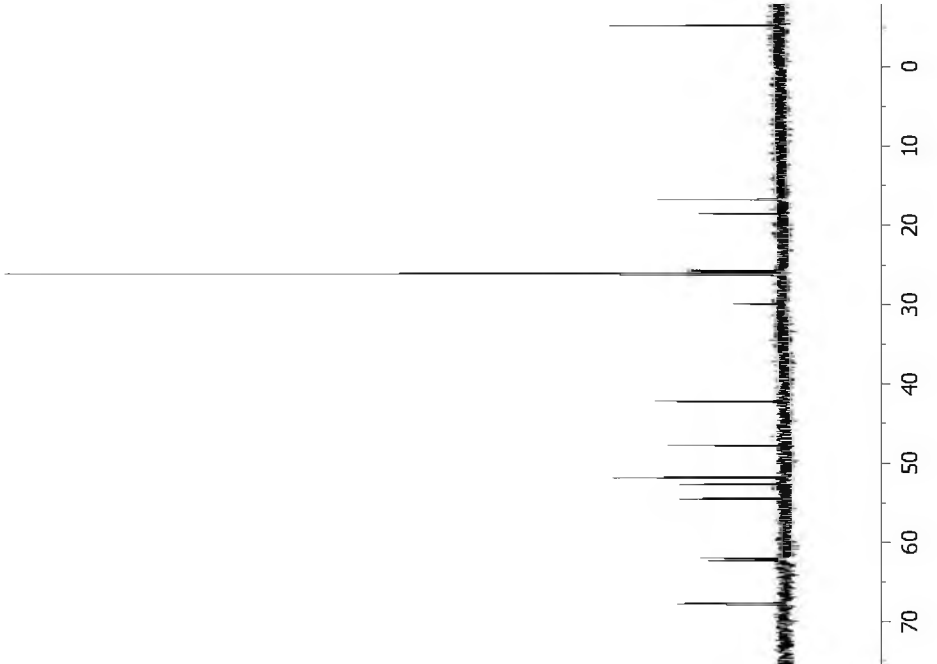


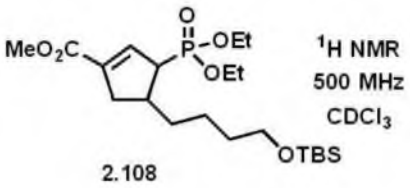

7.51
12.81
8.16
1.12
2.38
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0



2.107

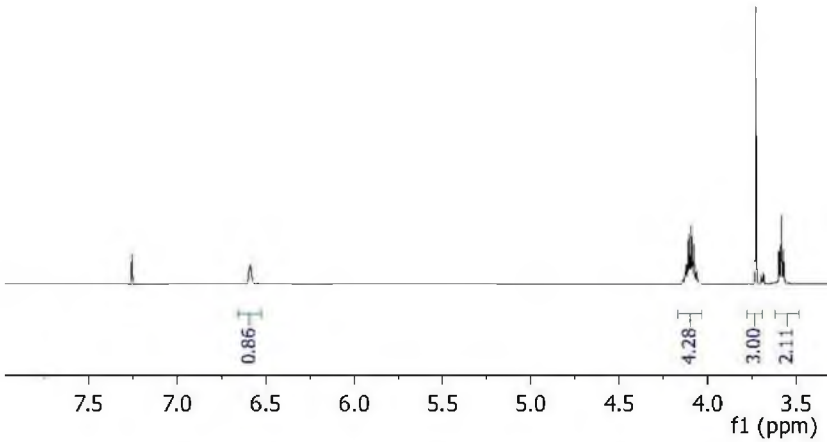
^{13}C NMR
75 MHz
$CDCl_3$


0
10
20
30
40
50
60
70

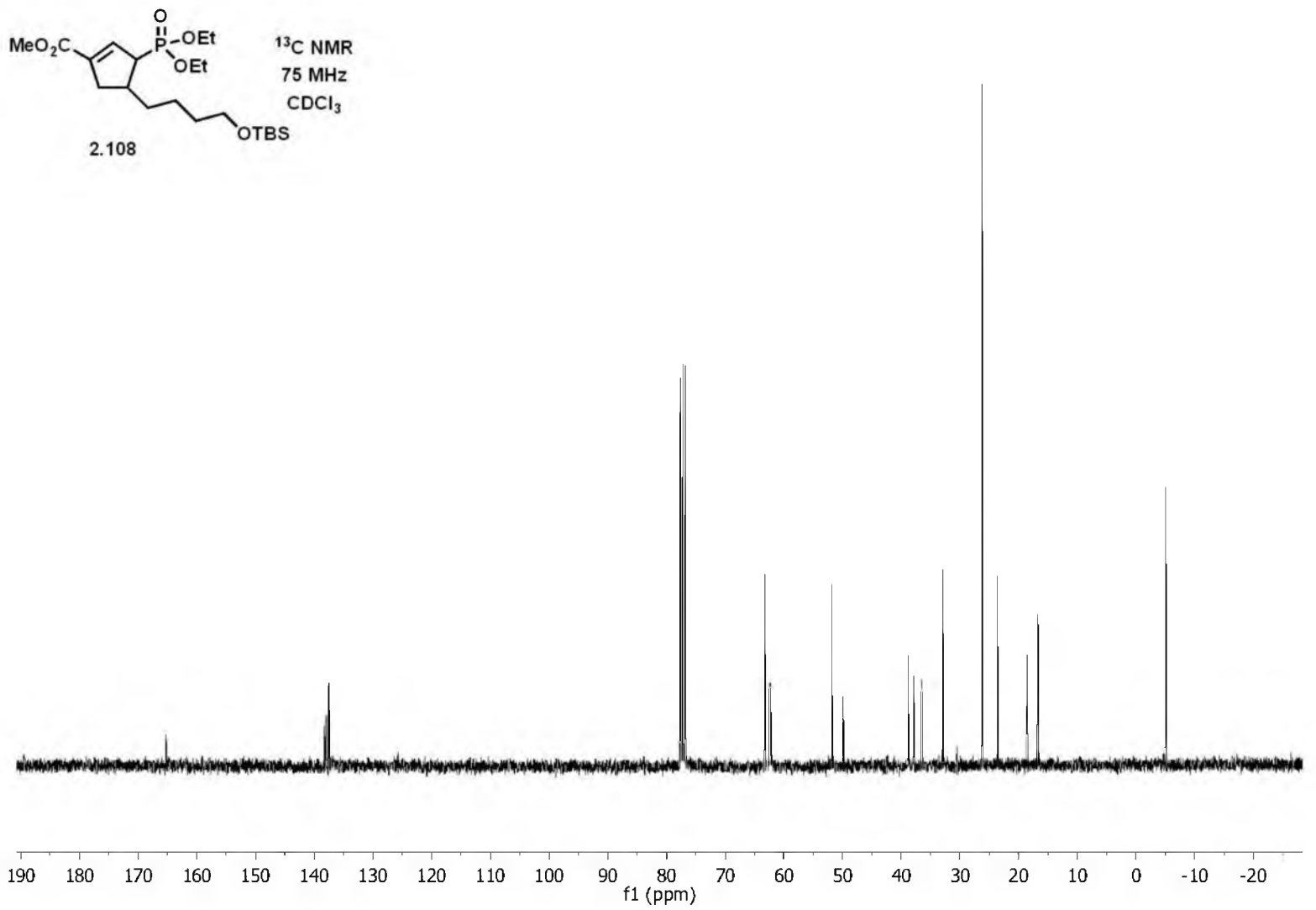


2.108

^{1}H NMR
500 MHz
$CDCl_3$

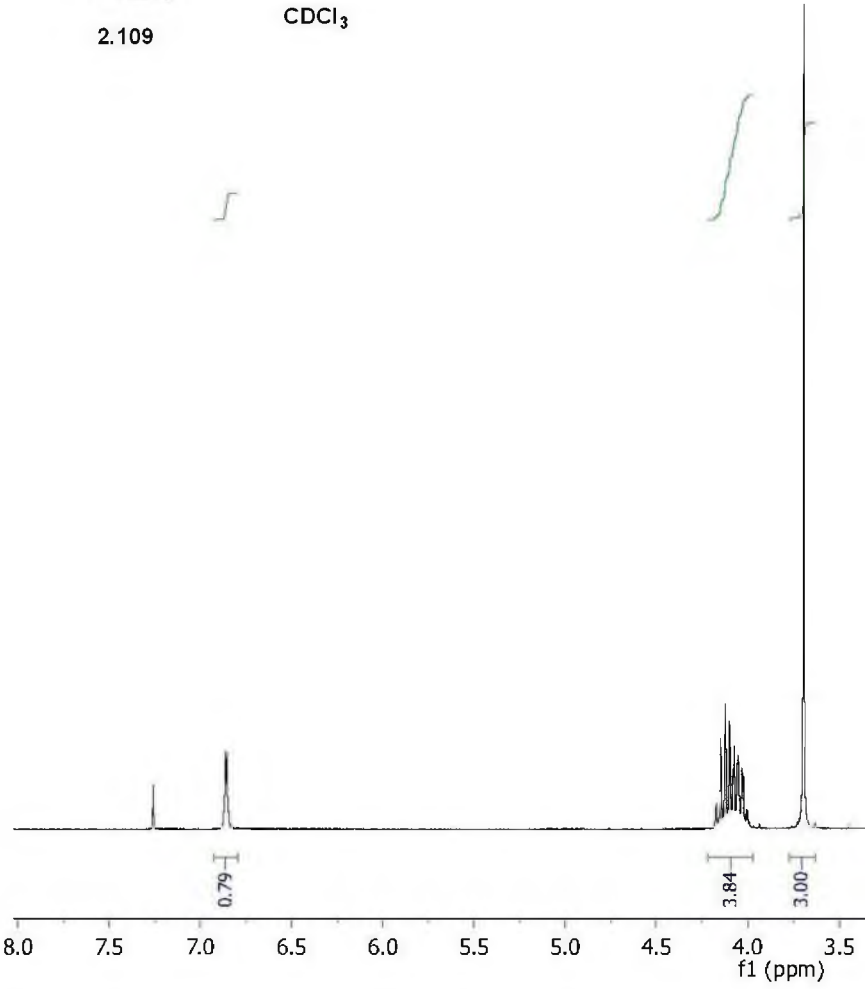


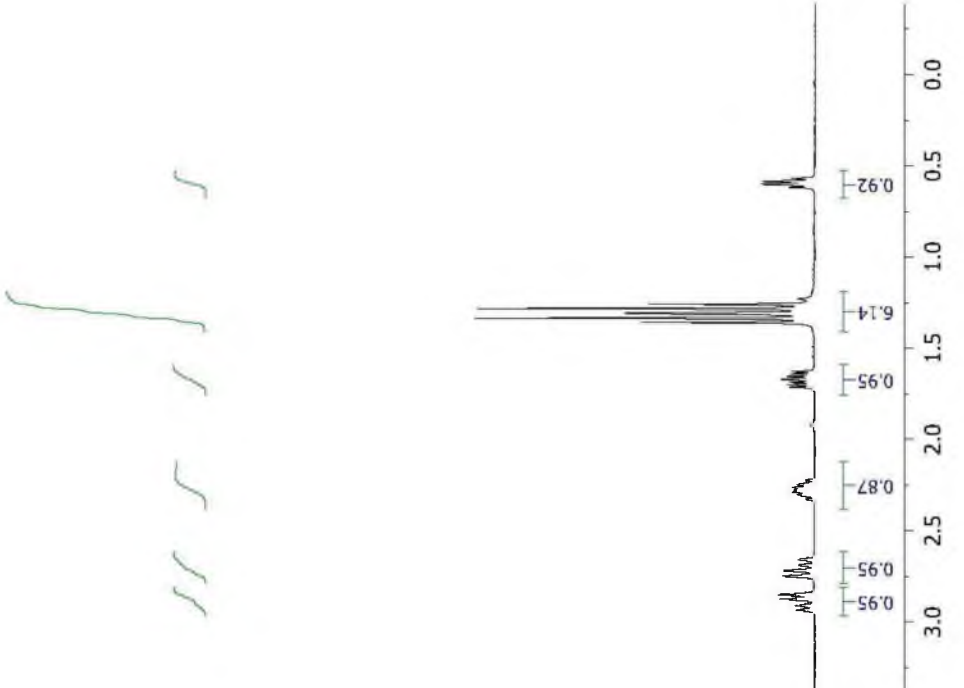
1.88
0.86
0.82
3.08
3.25
6.73
9.54
5.60
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


MeO2C
O
P
OEt
OEt
OTBS
2.108
13C NMR
75 MHz
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

2.109

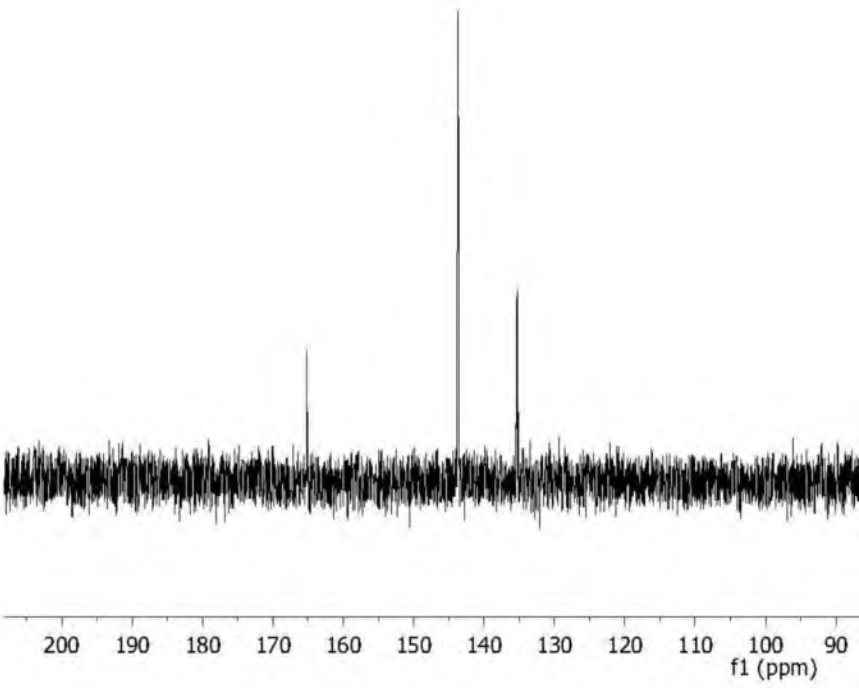
^{1}H NMR
300 MHz
$CDCl_3$

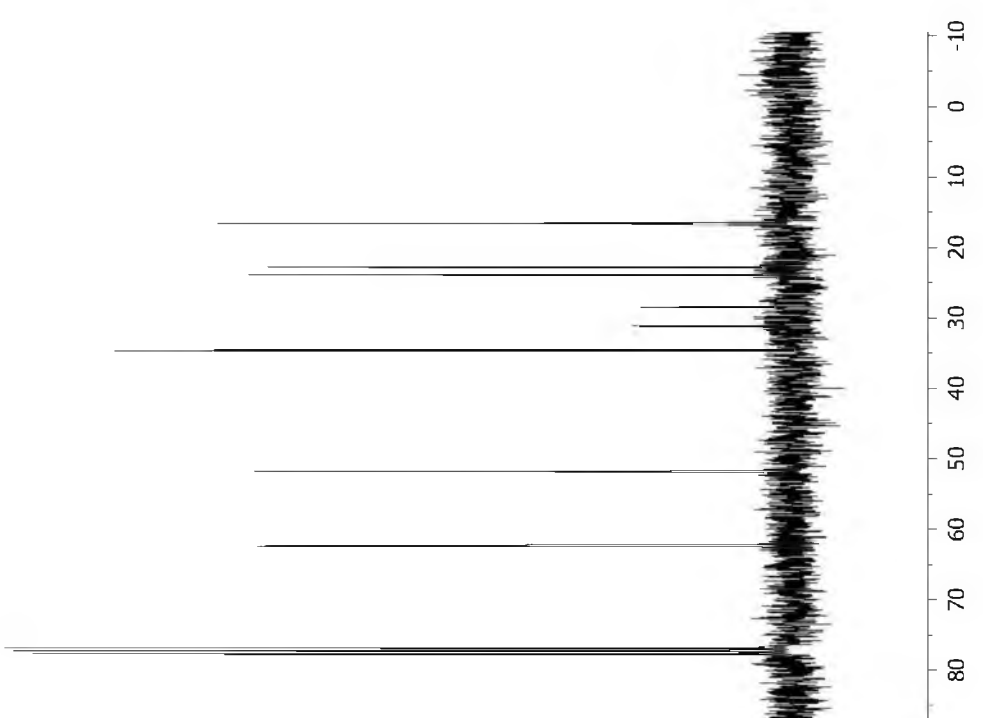


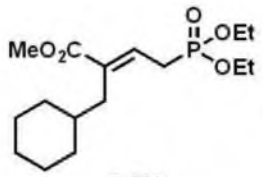

0.92
6.14
0.95
0.87
0.95
0.95
0.0
0.5
1.0
1.5
2.0
2.5
3.0

2.109

^{13}C NMR
75 MHz
$CDCl_3$

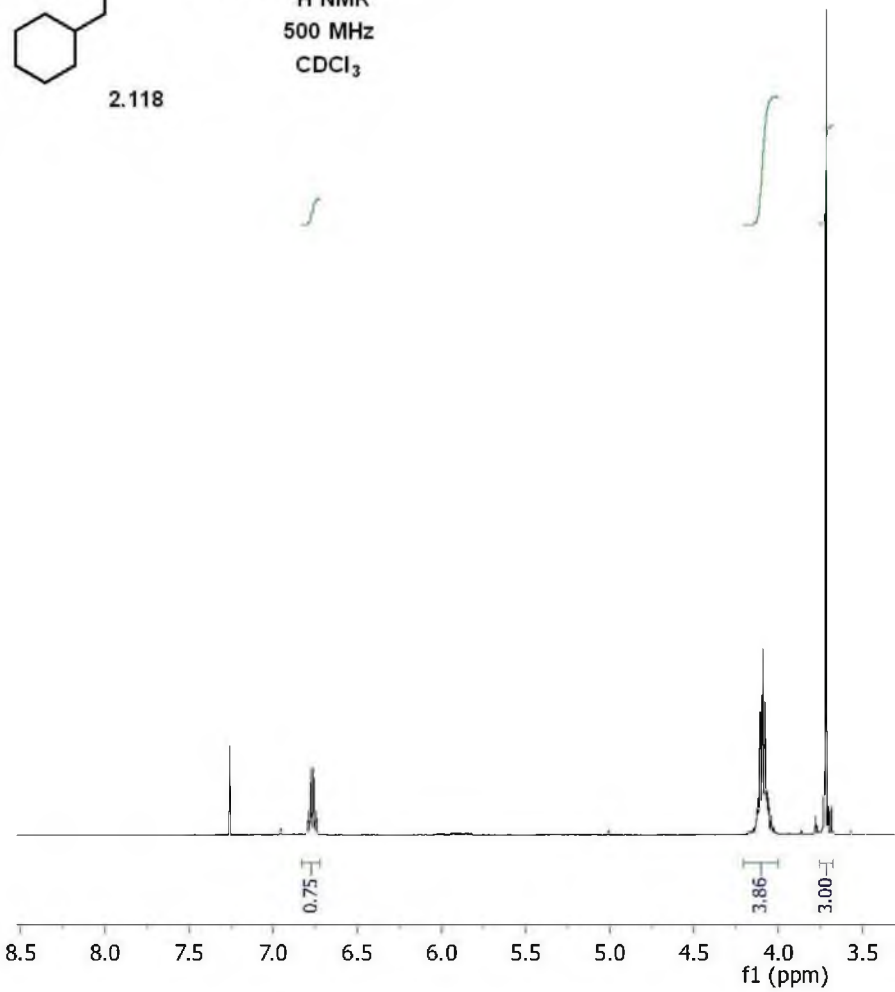


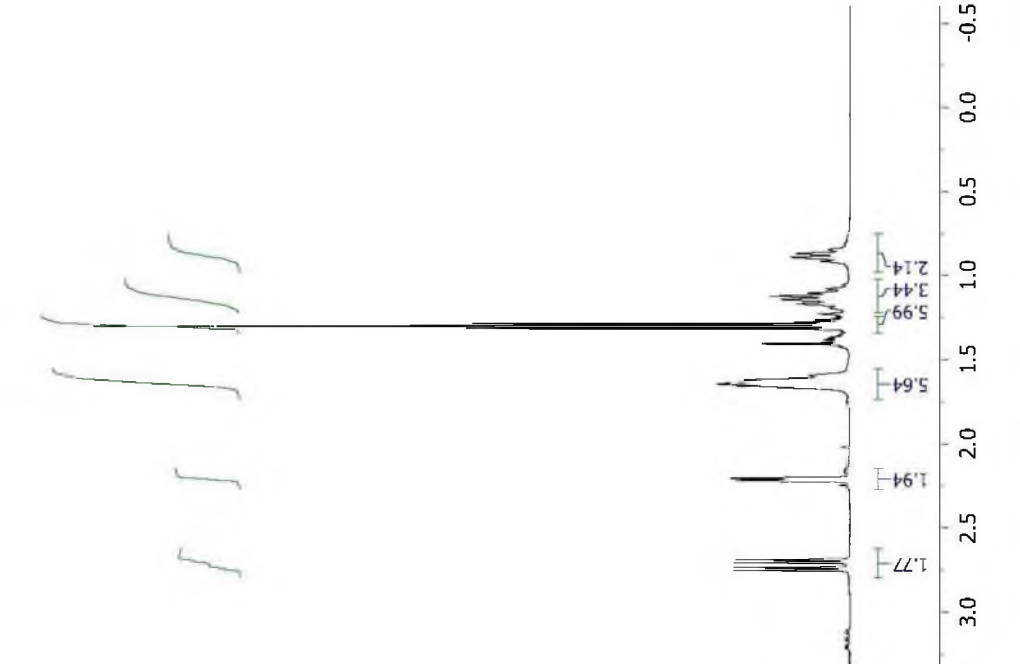

-10
0
10
20
30
40
50
60
70
80

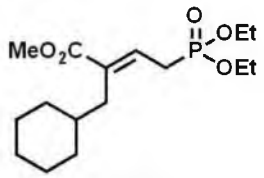


2.118

^{1}H NMR
500 MHz
$CDCl_3$

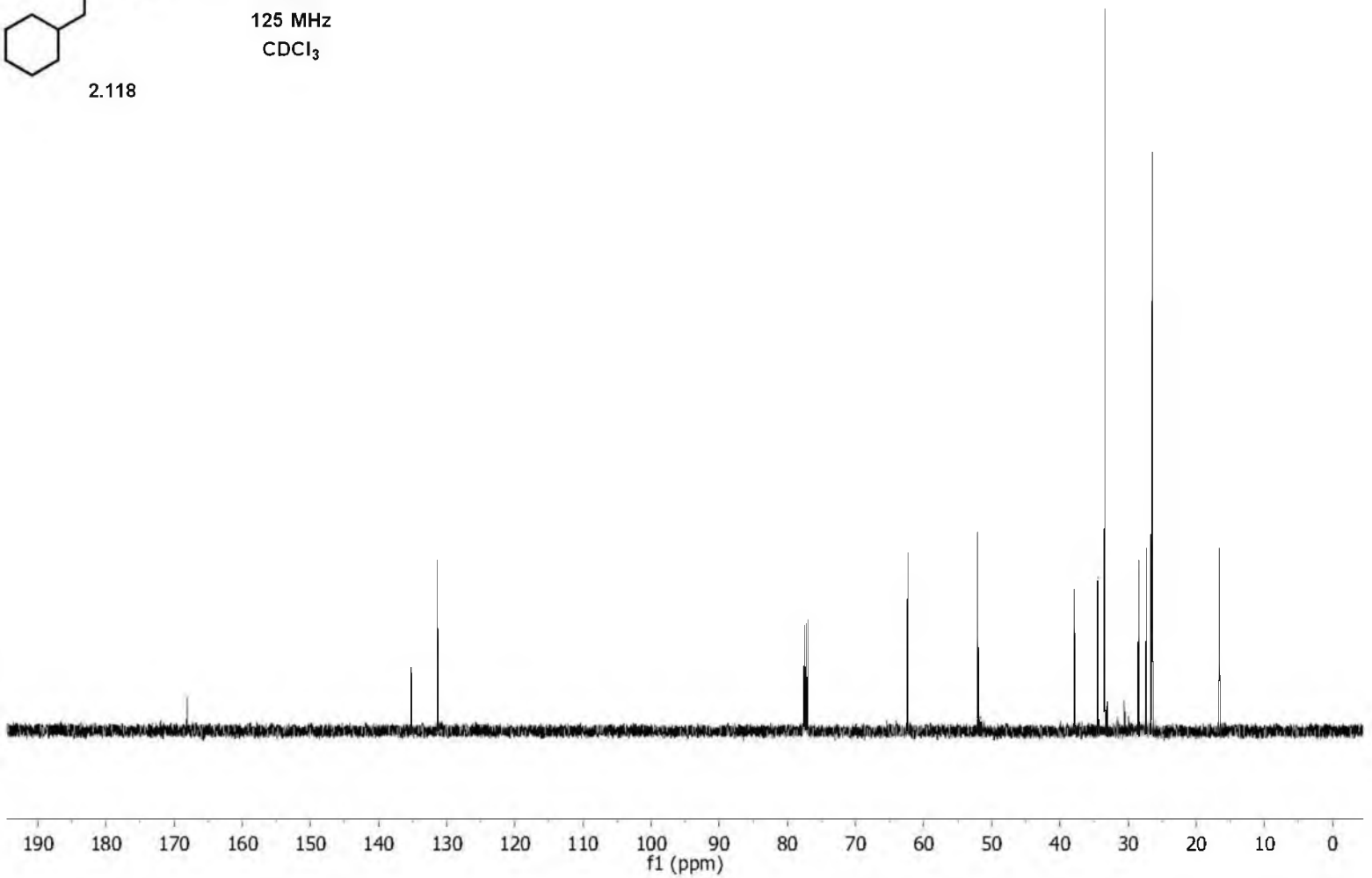


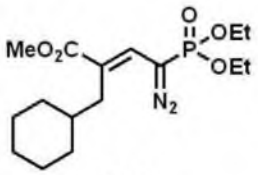

3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1.77
1.94
5.64
5.99
3.44
2.14



2.118

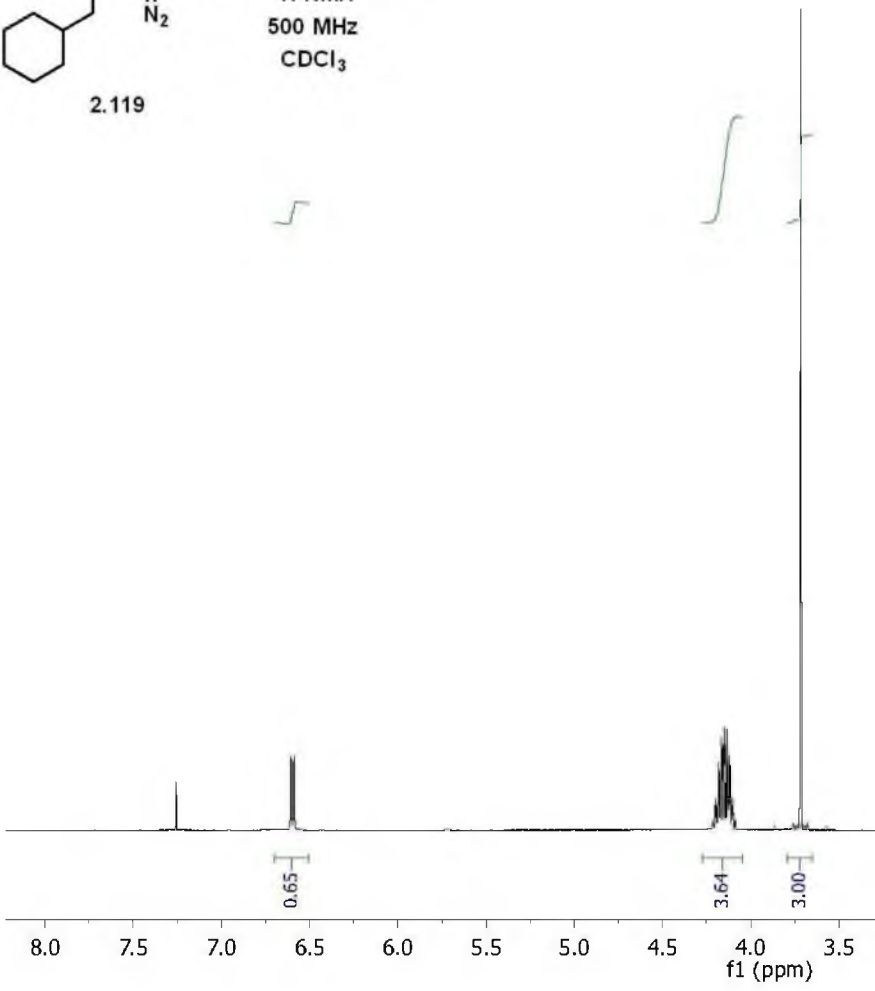
^{13}C NMR
125 MHz
$CDCl_3$

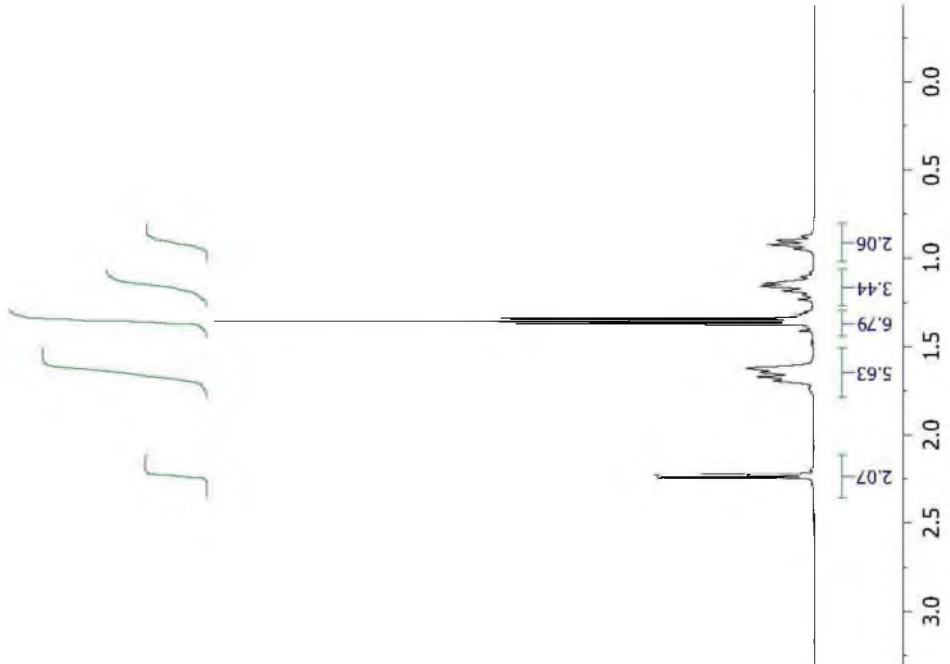


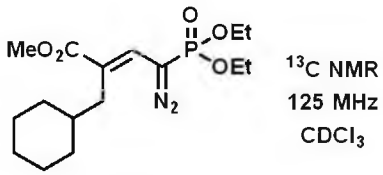


2.119

^{1}H NMR
500 MHz
$CDCl_3$

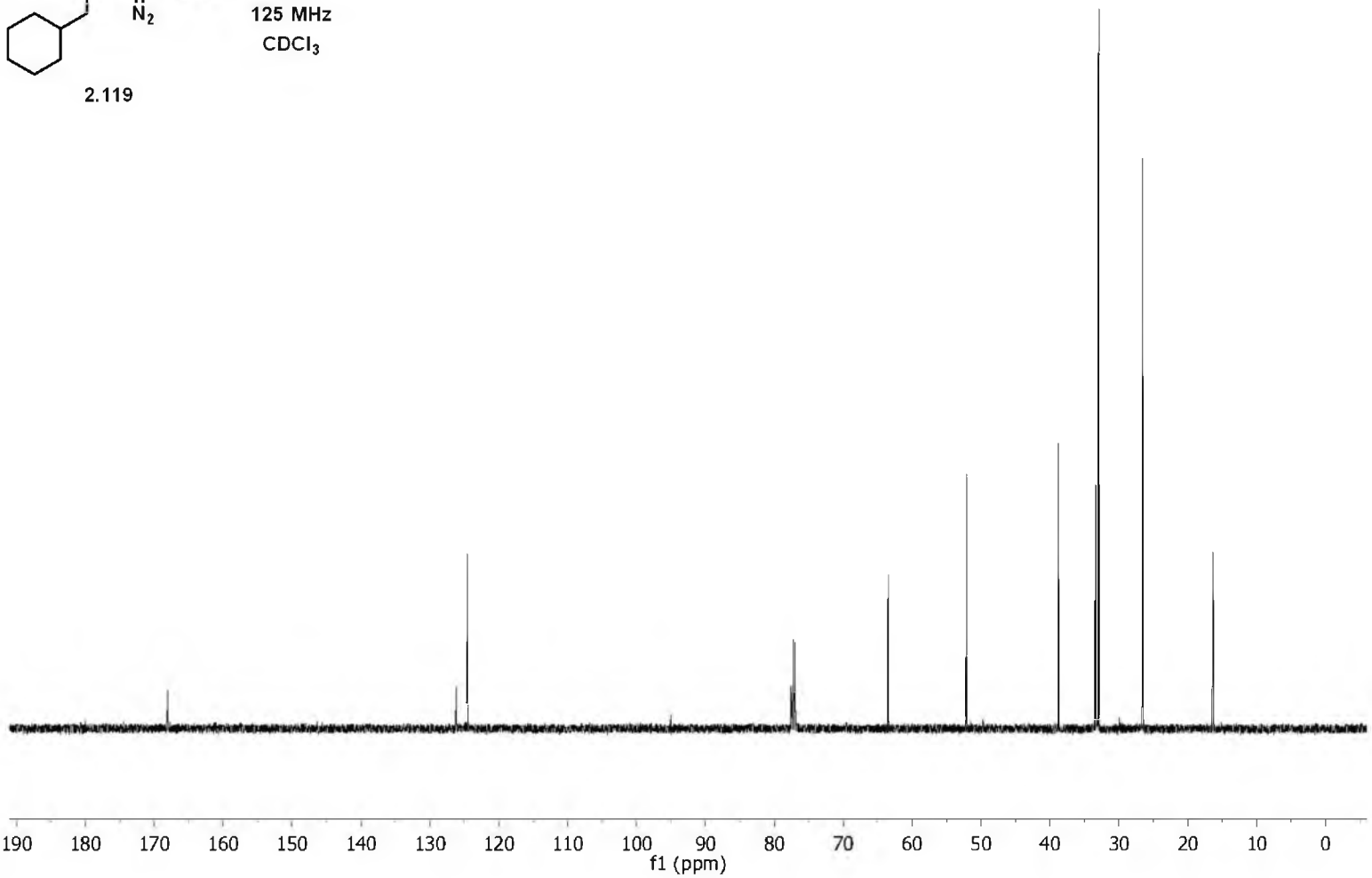


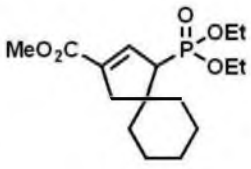

2.07
5.63
6.79
3.44
2.06
3.0
2.5
2.0
1.5
1.0
0.5
0.0



2.119

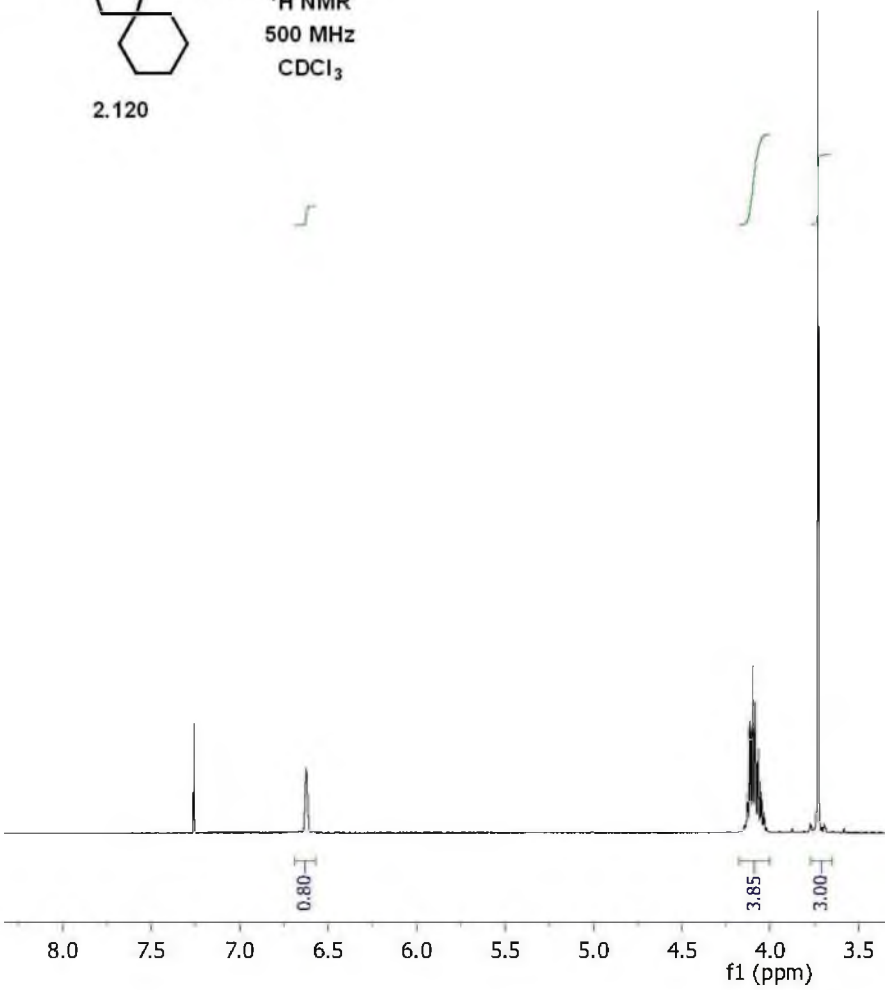
^{13}C NMR
125 MHz
$CDCl_3$

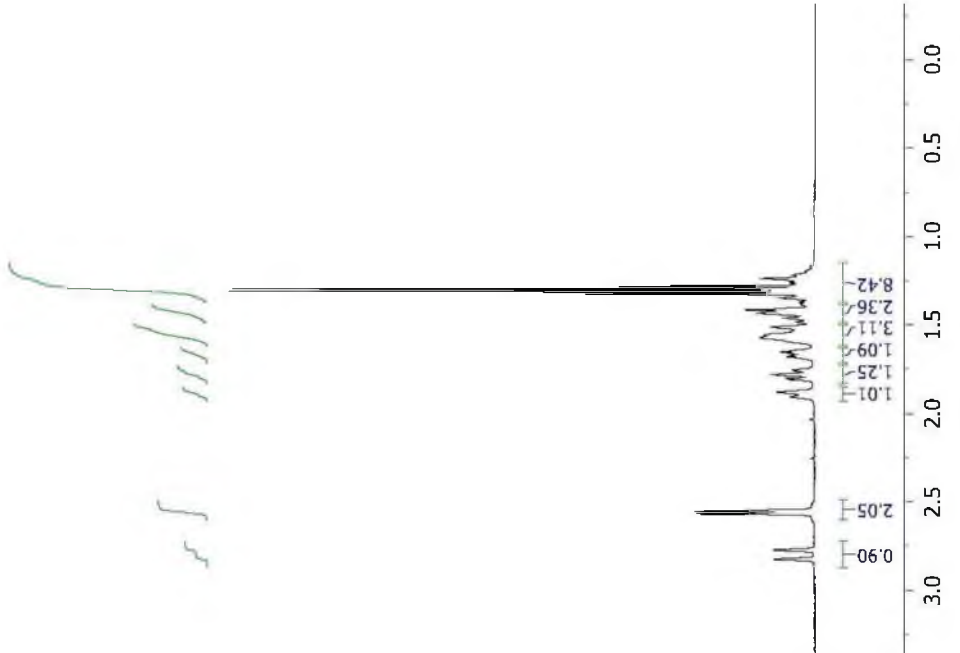


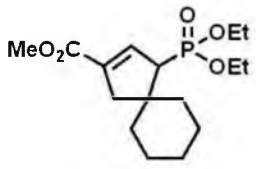


2.120

^{1}H NMR
500 MHz
$CDCl_3$

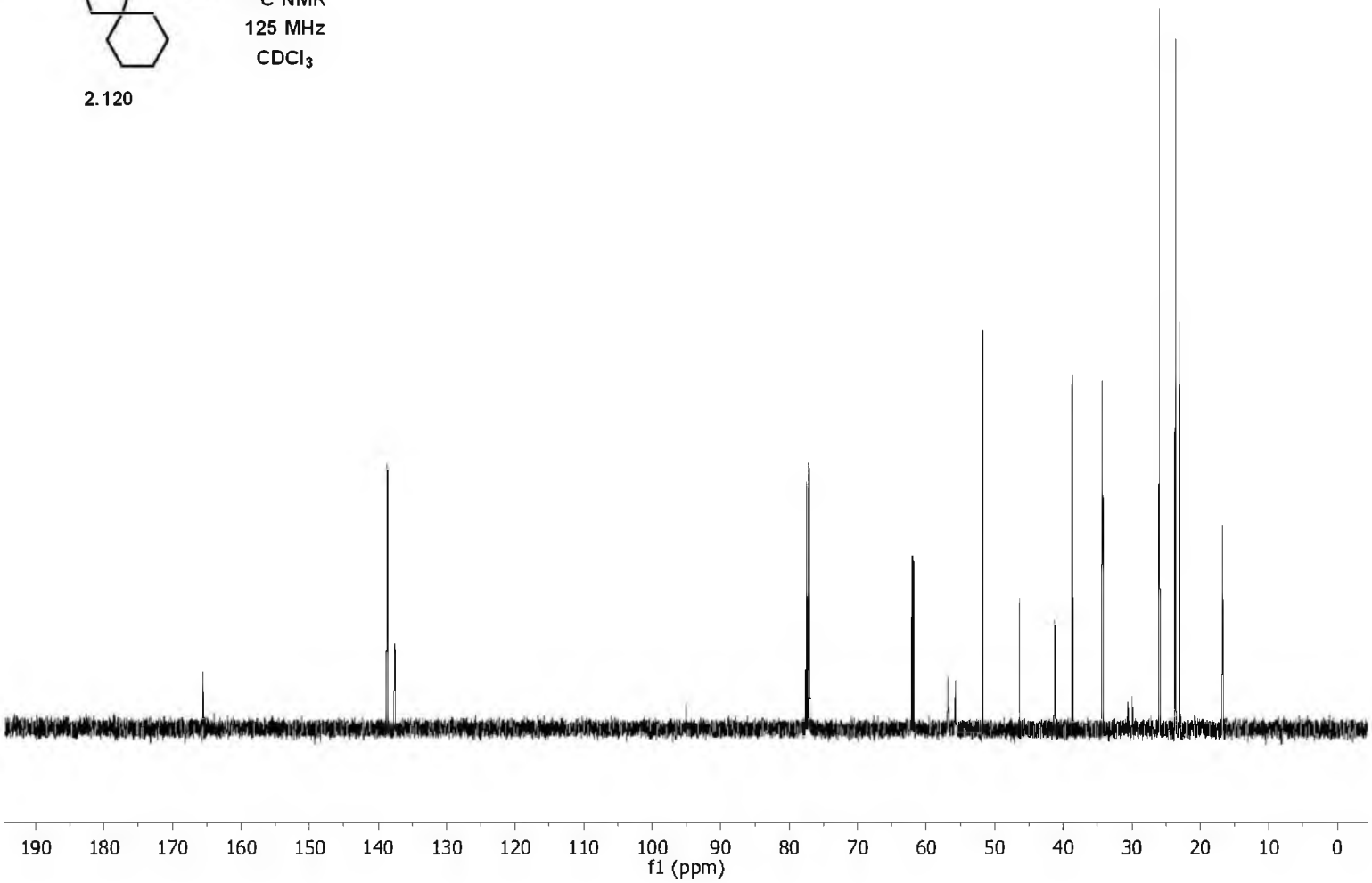


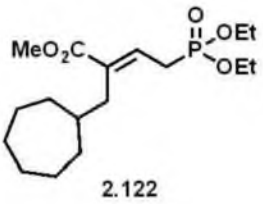

8.42
2.36
3.11
1.09
1.25
1.01
2.05
0.90
3.0
2.5
2.0
1.5
1.0
0.5
0.0



2.120

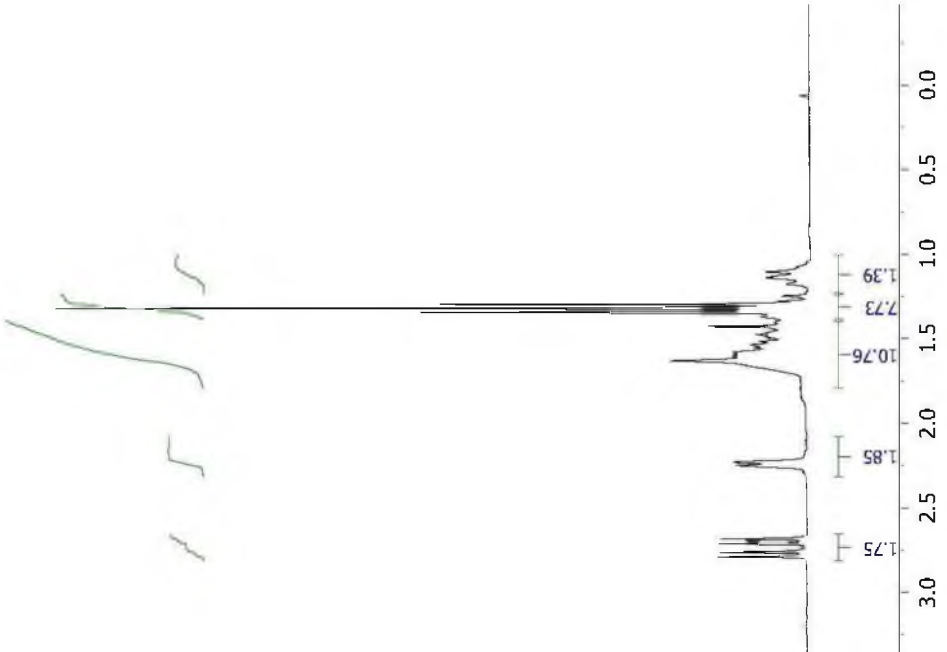
^{13}C NMR
125 MHz
$CDCl_3$

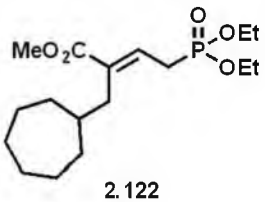




2.122

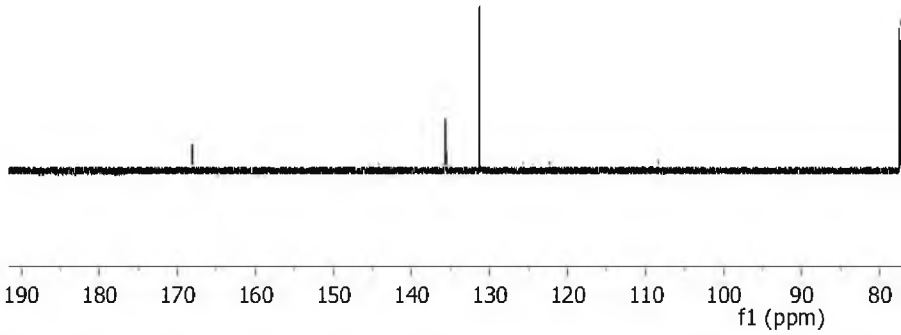
^{1}H NMR
300 MHz
$CDCl_3$

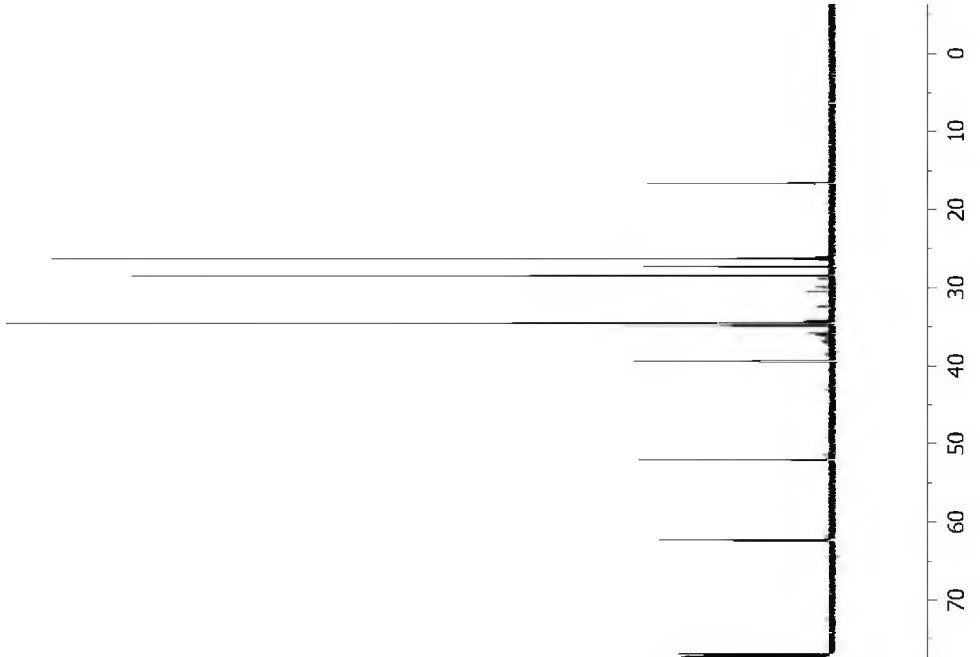

0.0
0.5
1.0
1.5
2.0
2.5
3.0
1.39
7.73
10.76
1.85
1.75

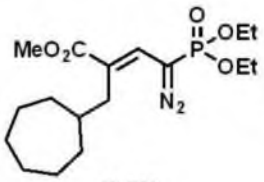


2.122

^{13}C NMR
125 MHz
$CDCl_3$

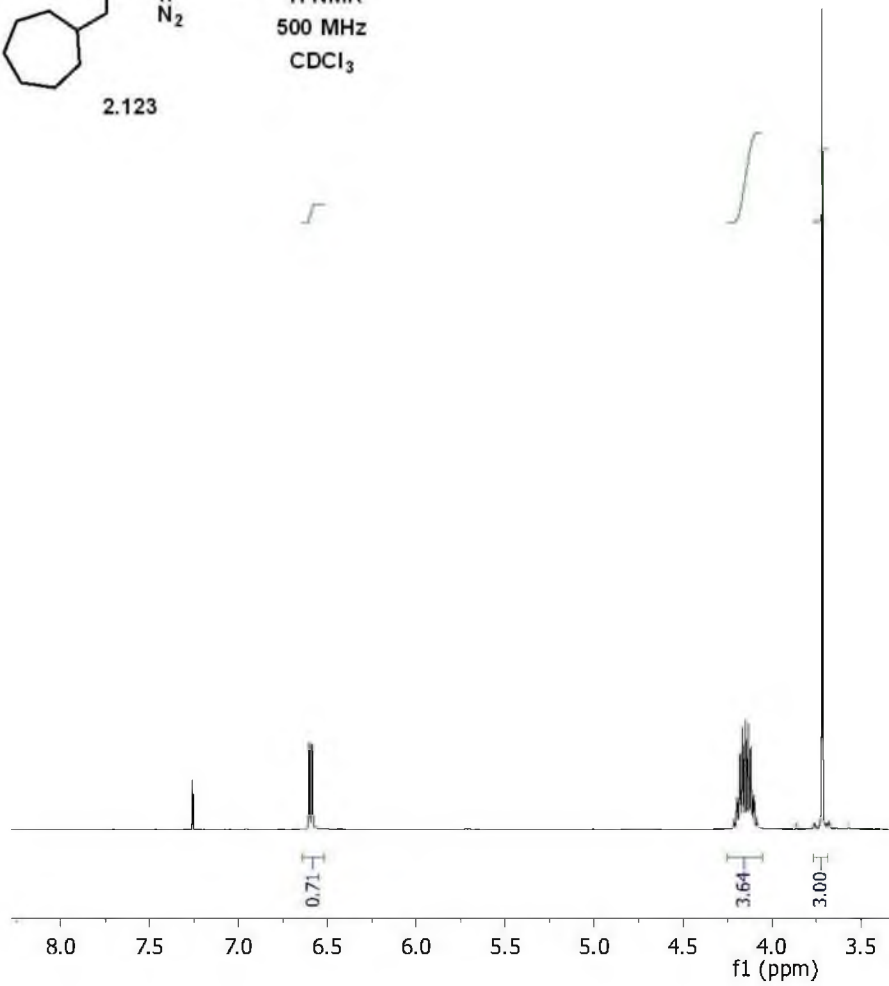


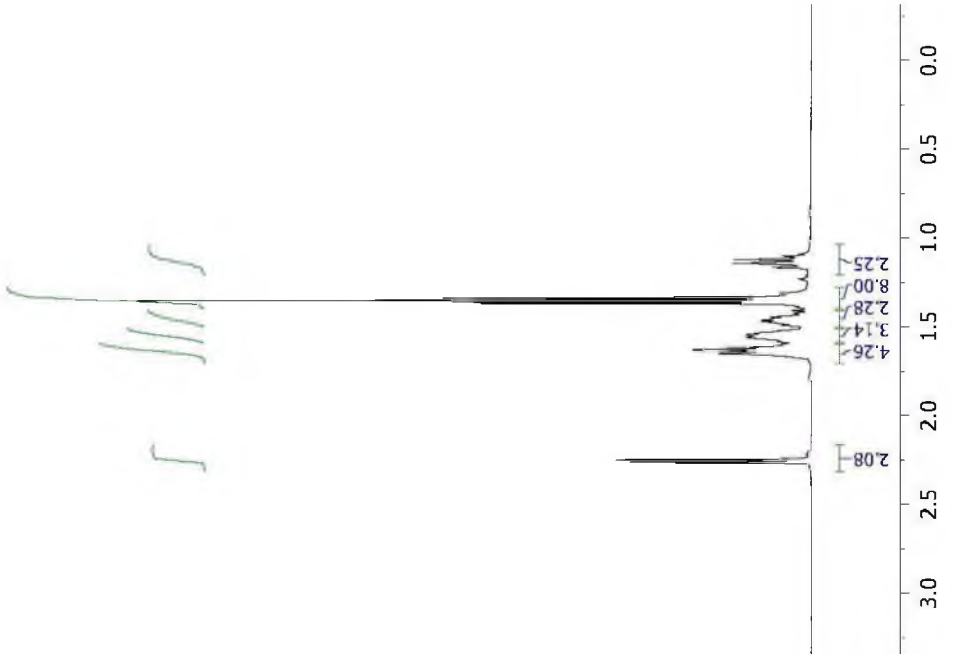

0
10
20
30
40
50
60
70

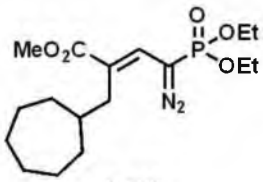


2.123

^{1}H NMR
500 MHz
$CDCl_3$

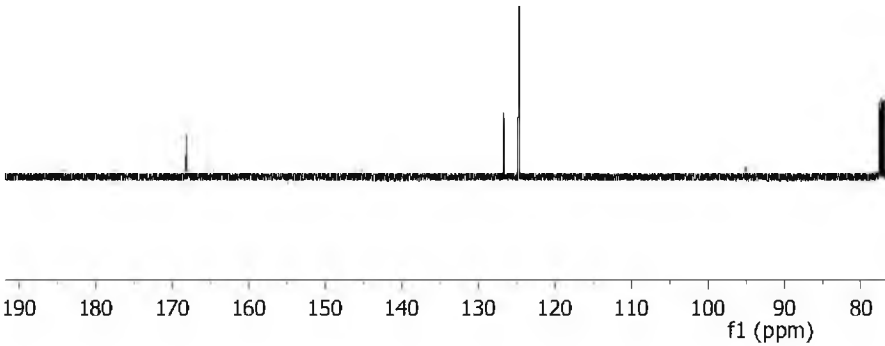


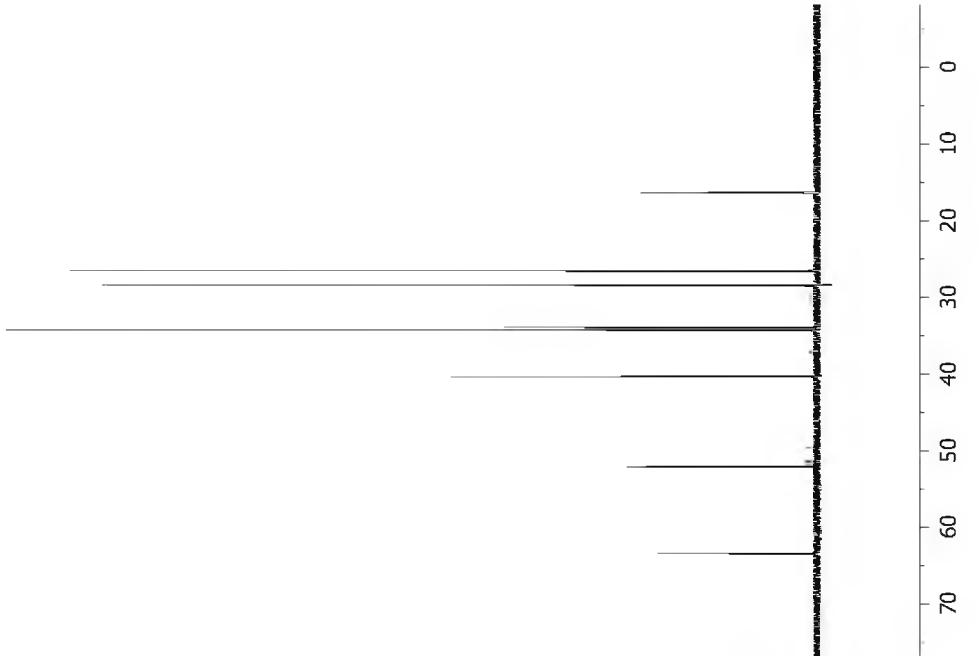

2.25
8.00
2.28
3.14
4.26
2.08
0.0
0.5
1.0
1.5
2.0
2.5
3.0

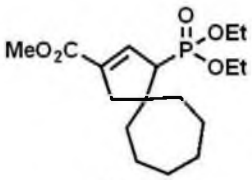


2.123

^{13}C NMR
125 MHz
$CDCl_3$

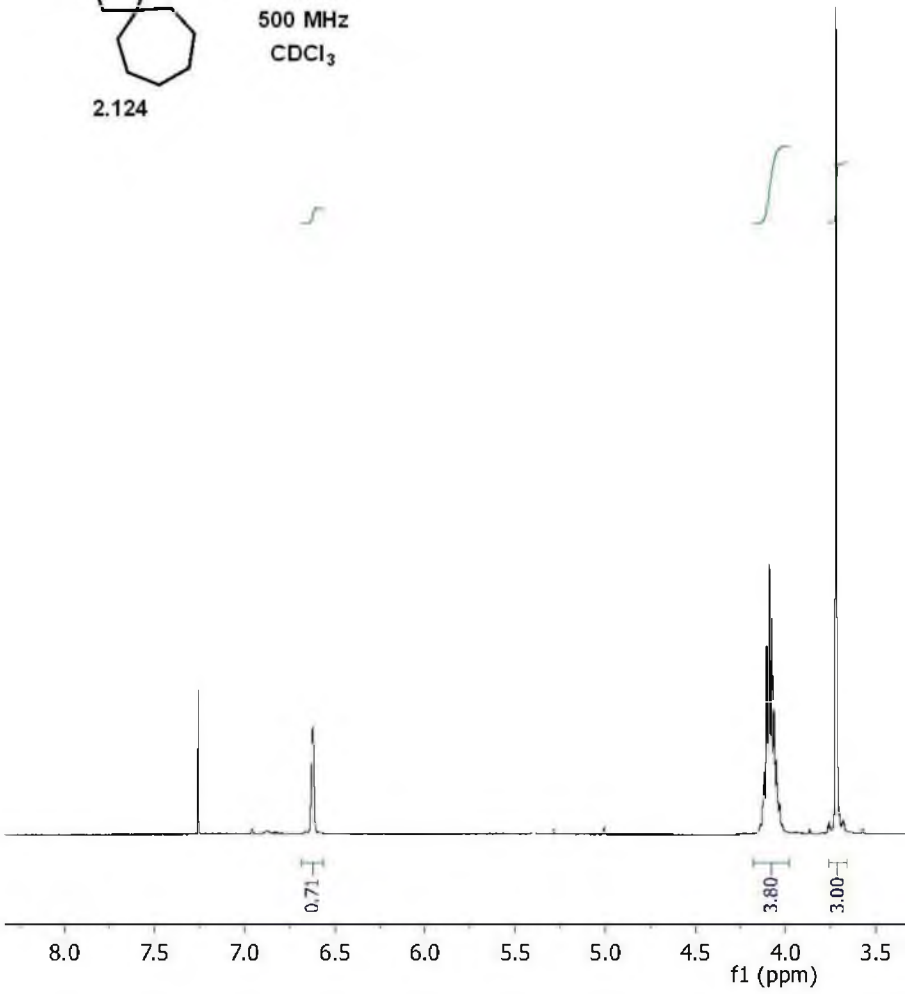


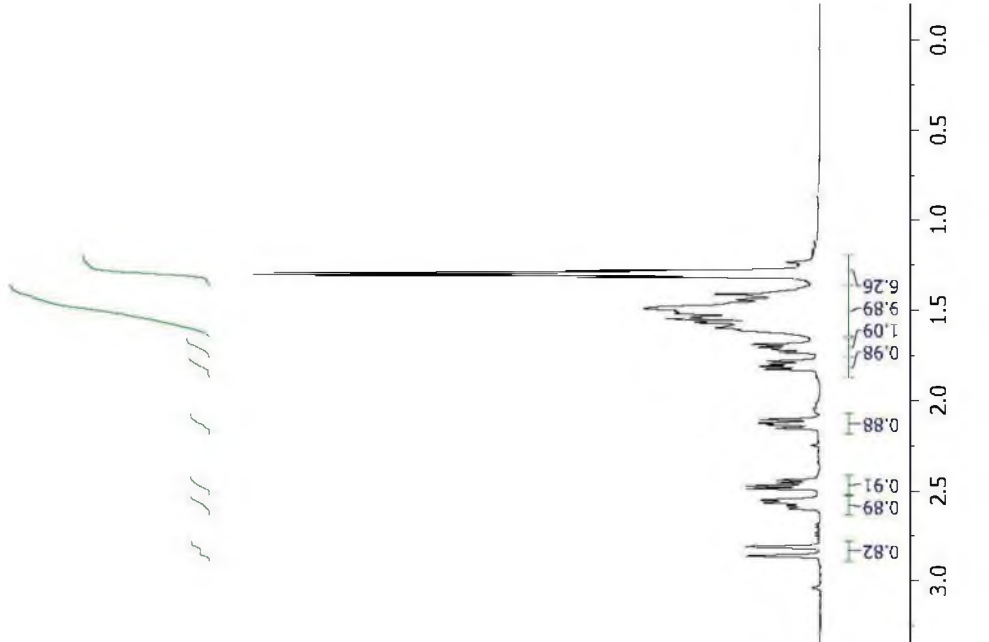

0
10
20
30
40
50
60
70

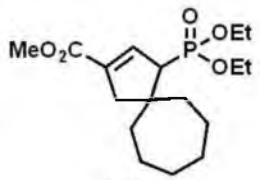


2.124

^{1}H NMR
500 MHz
$CDCl_3$

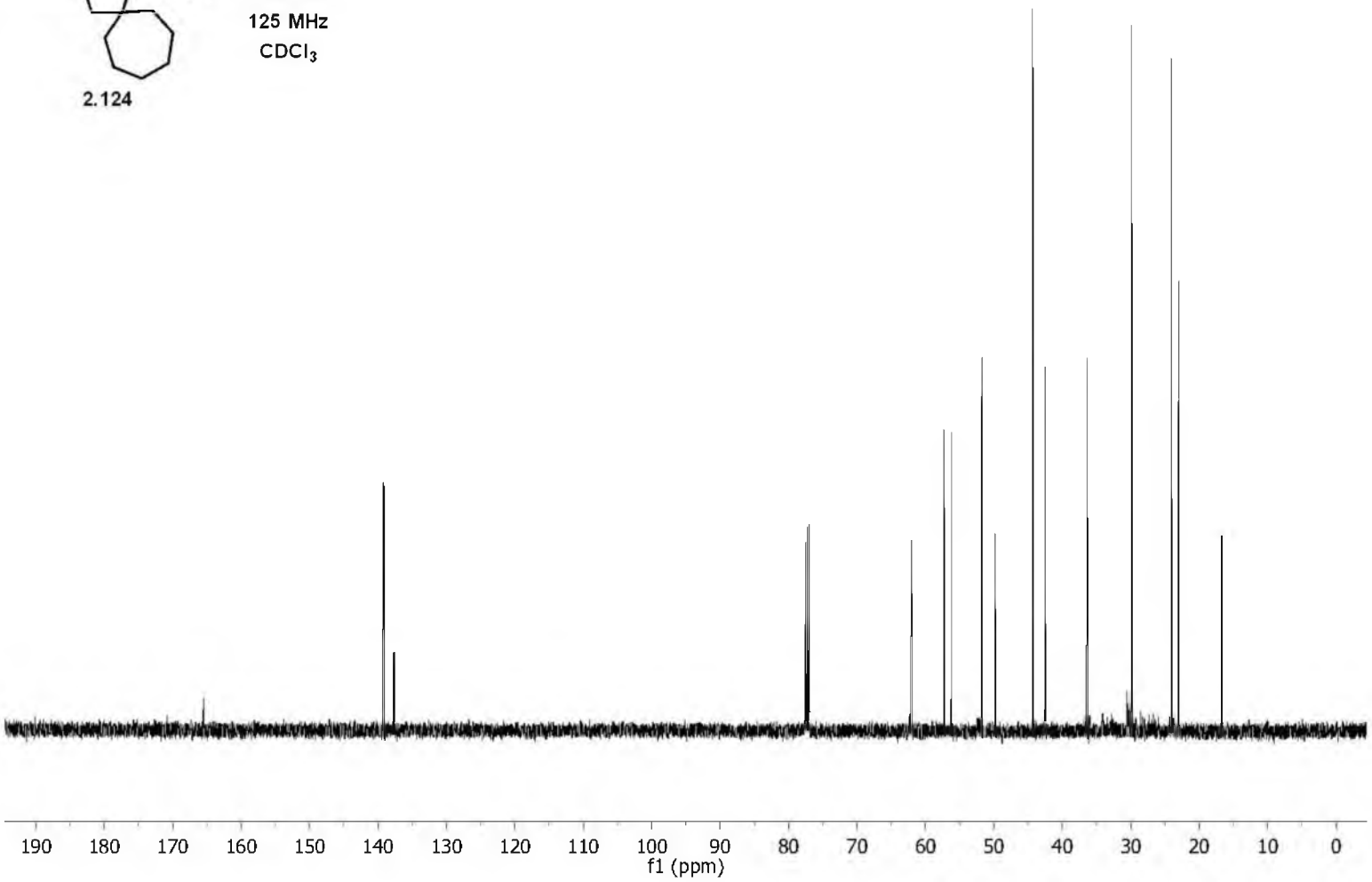


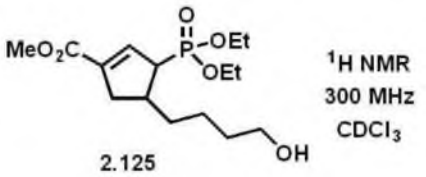

0.82
0.89
0.91
0.88
0.98
1.09
9.89
6.26
3.0
2.5
2.0
1.5
1.0
0.5
0.0



2.124

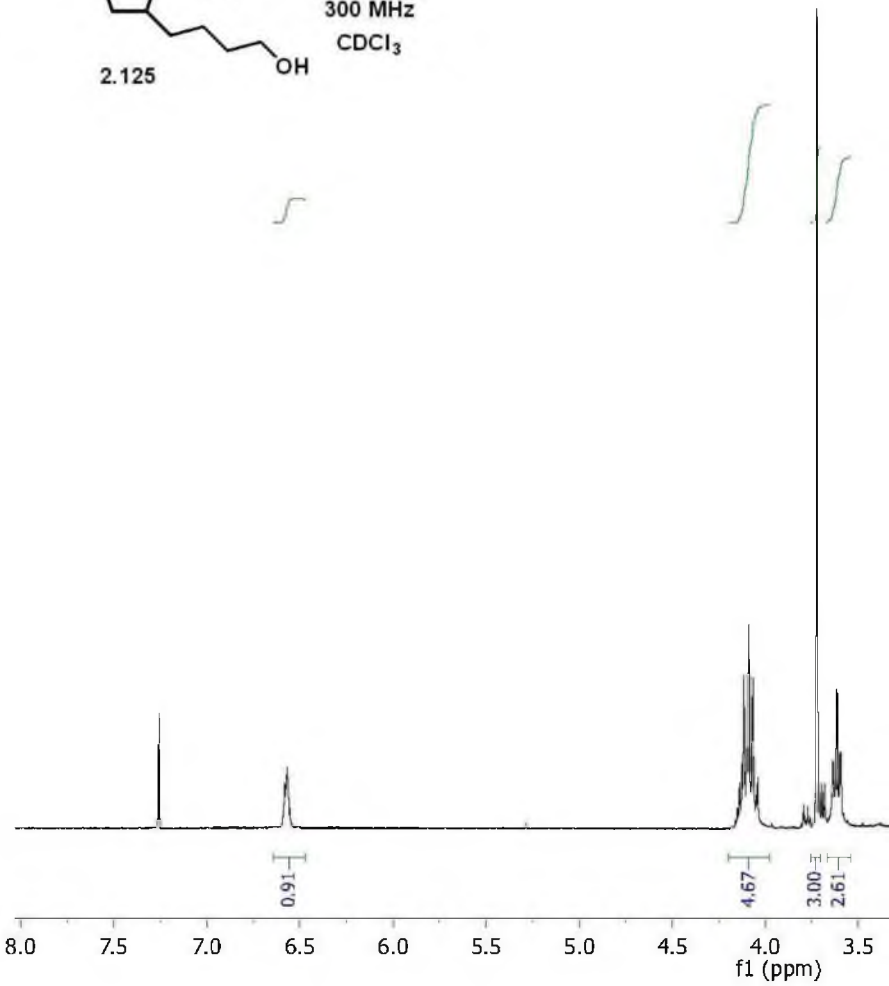
^{13}C NMR
125 MHz
$CDCl_3$



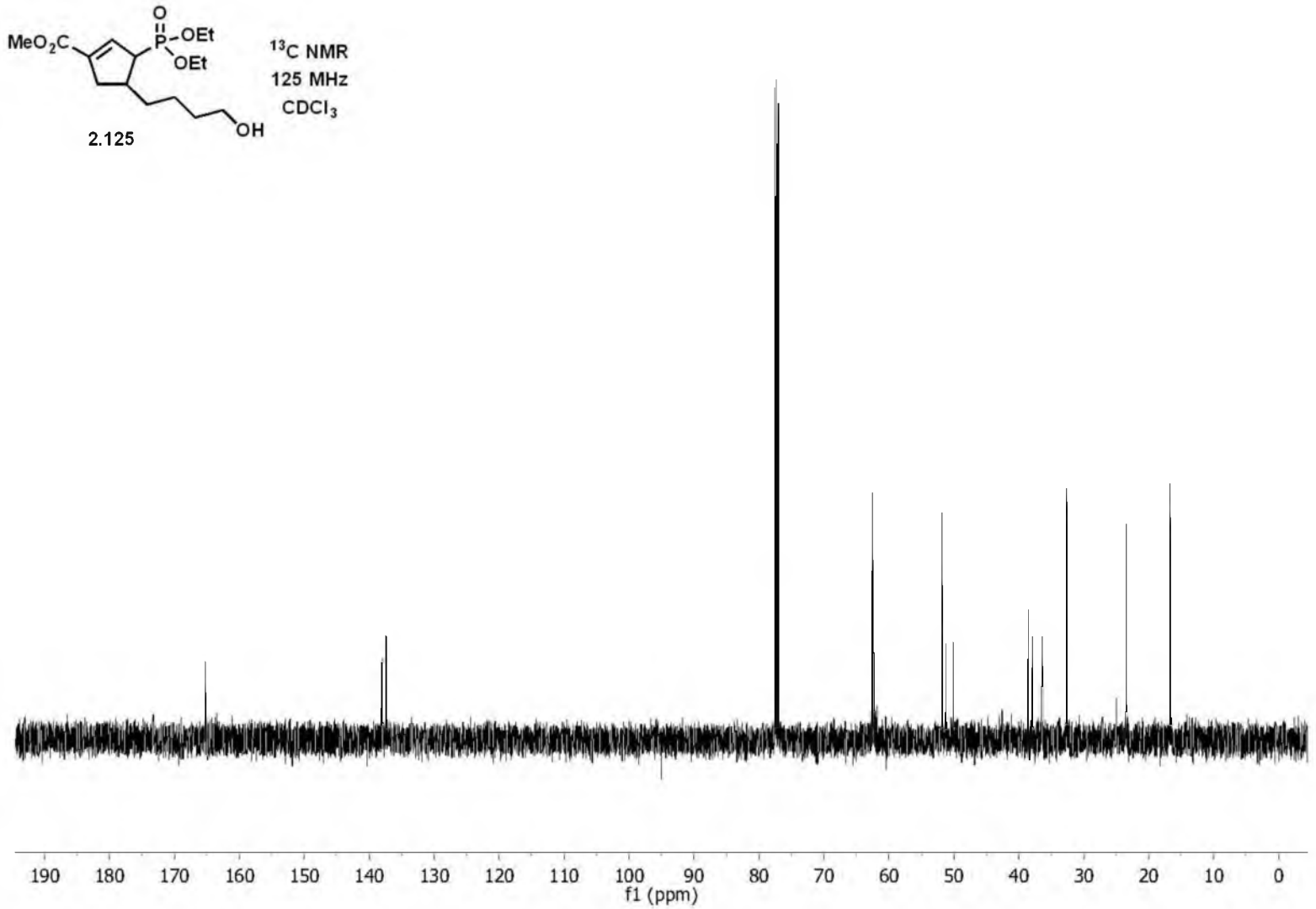


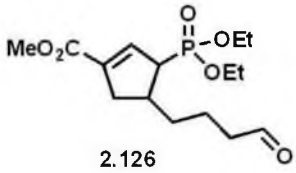
2.125

^{1}H NMR
300 MHz
$CDCl_3$



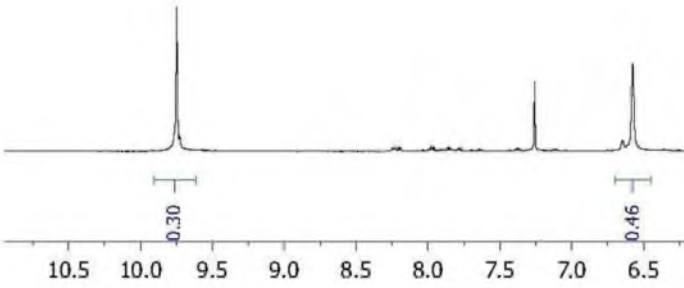
1.79
0.94
0.94
3.19
2.96
7.90
3.0
2.5
2.0
1.5
1.0
0.5
0.0

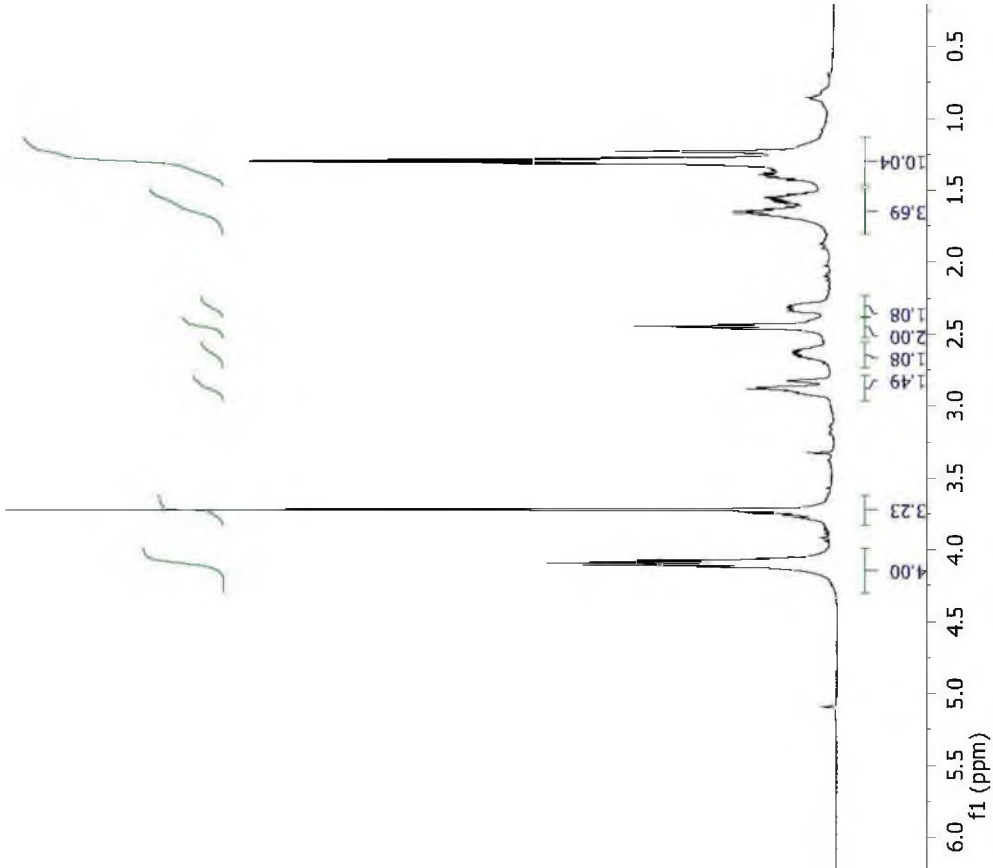

MeO2C
O
P
OEt
OEt
OH
2.125
13C NMR
125 MHz
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

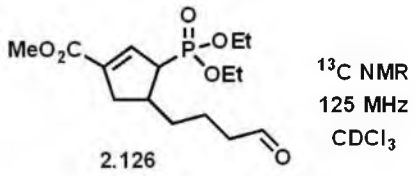


2.126

^{1}H NMR
500 MHz
$CDCl_3$

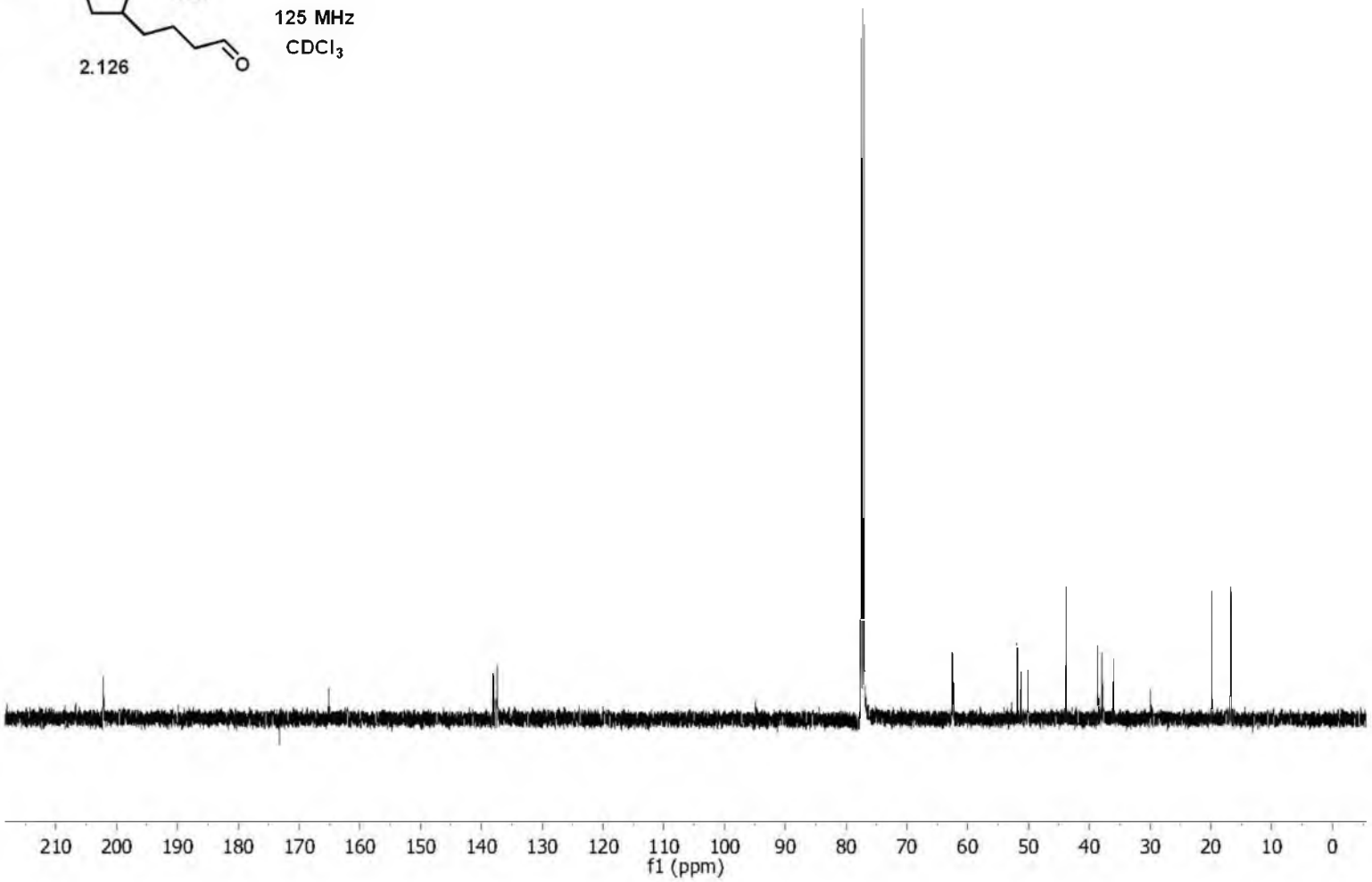


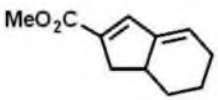

4.00
3.23
1.49
1.08
2.00
1.08
3.69
10.04
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



2.126

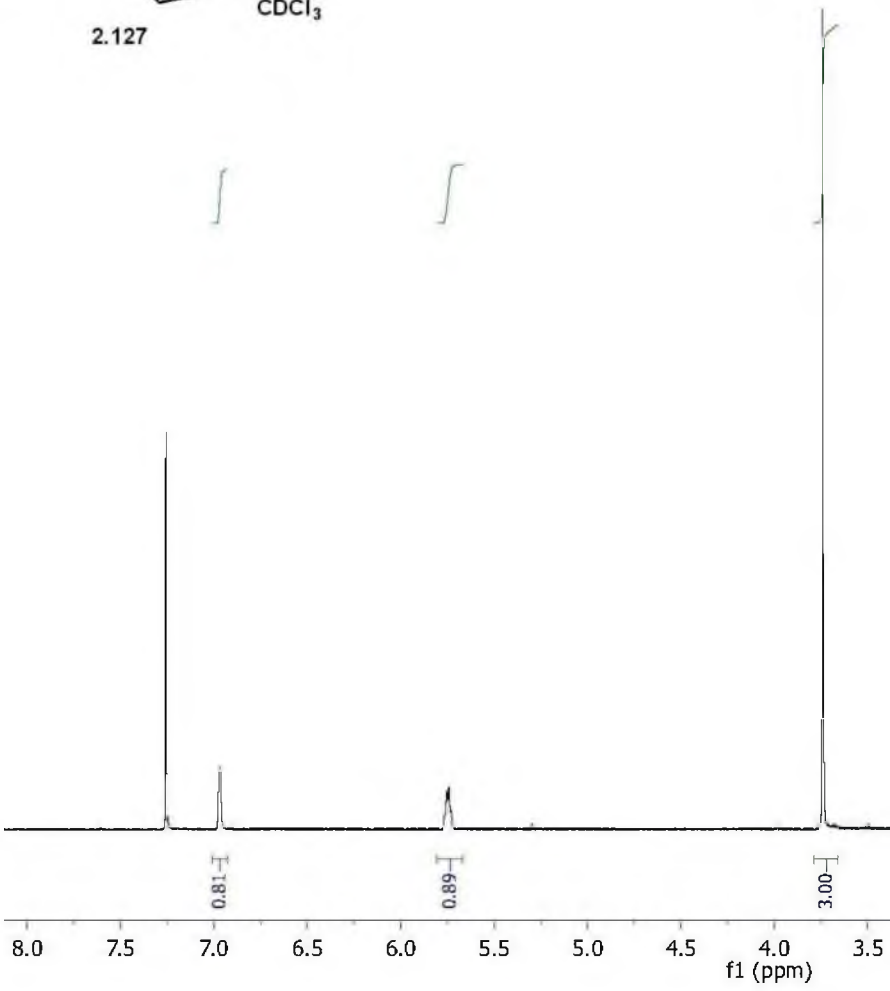
^{13}C NMR
125 MHz
$CDCl_3$



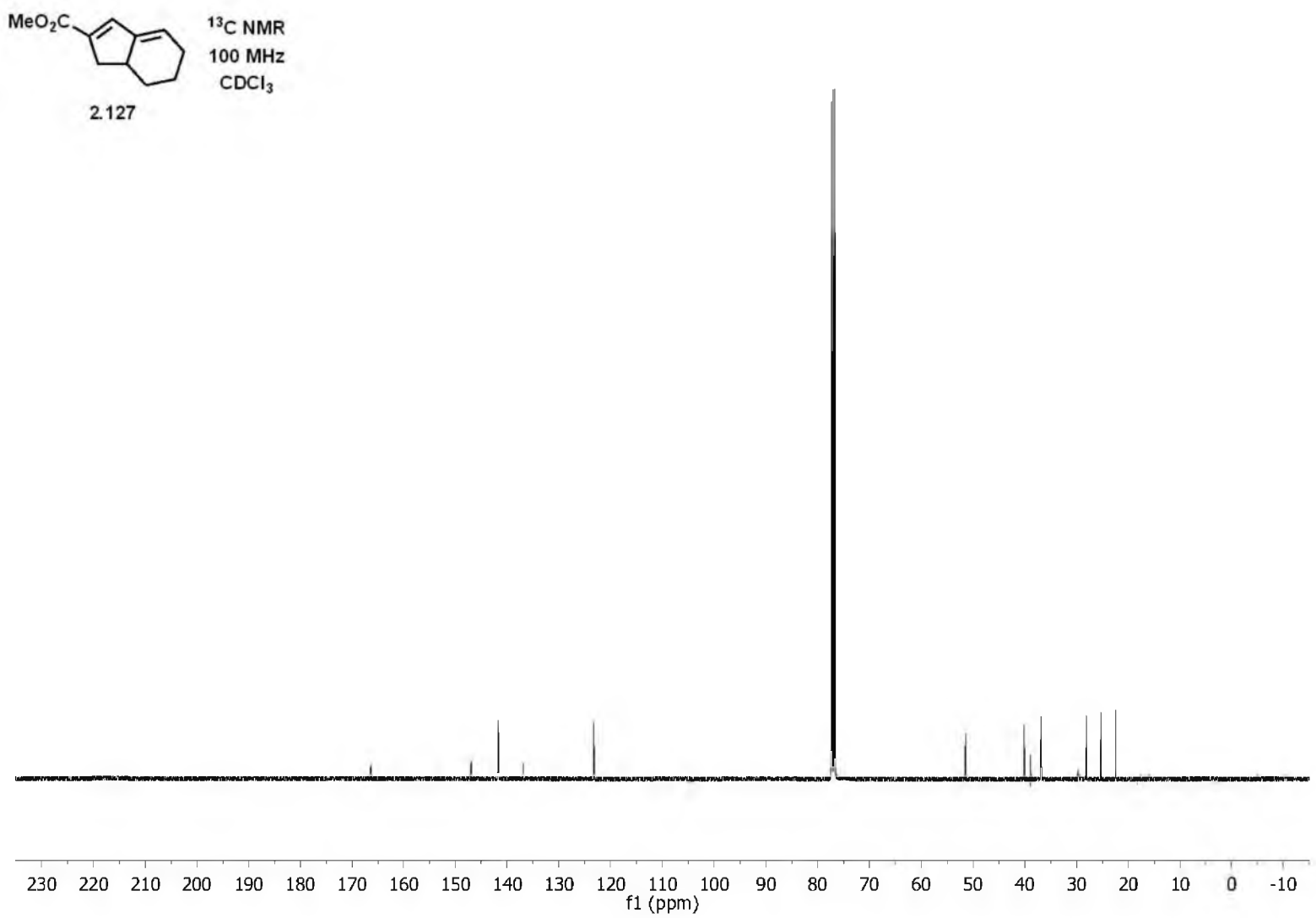


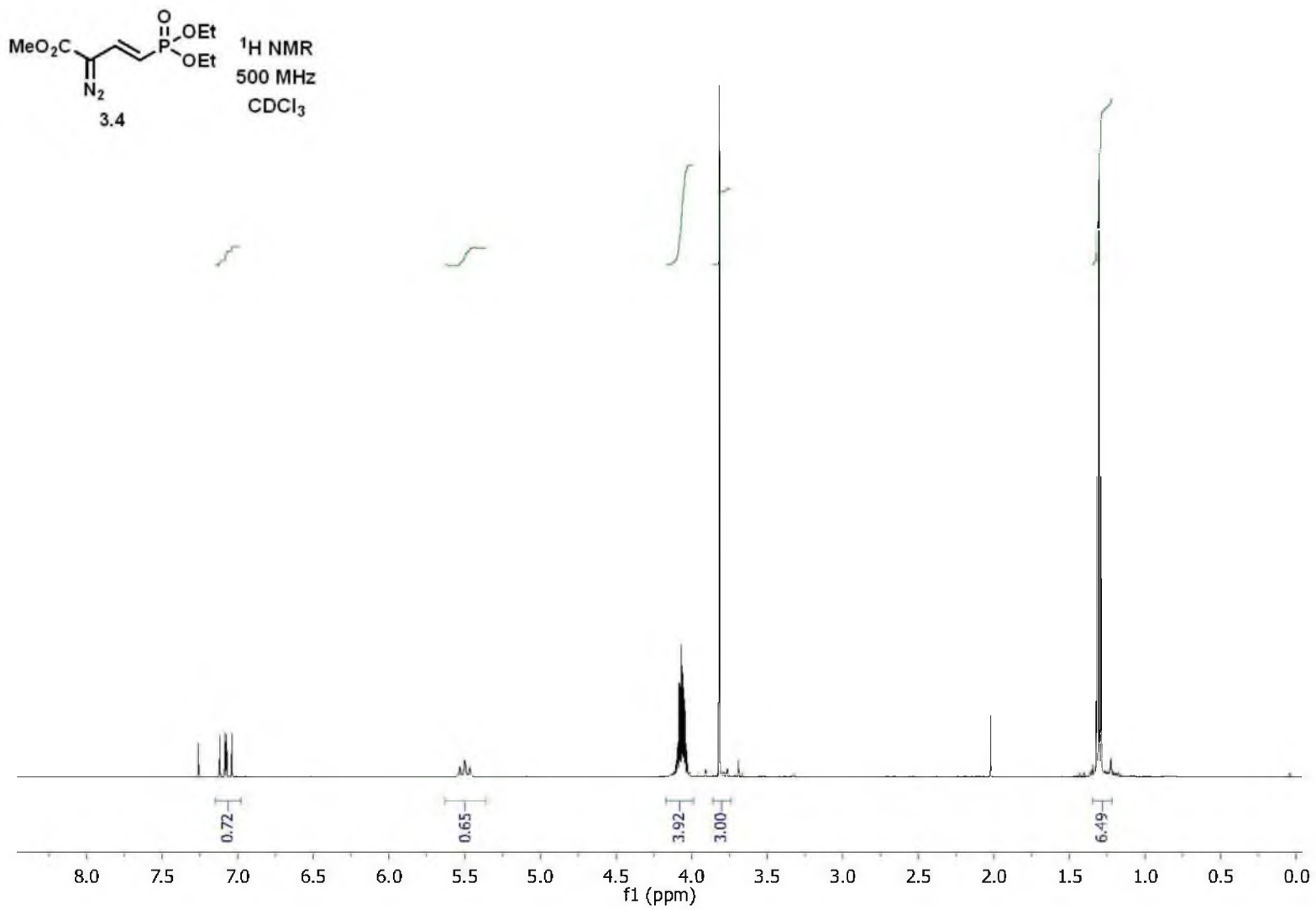
2.127

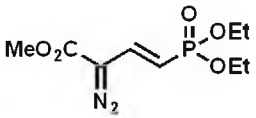
^{1}H NMR
300 MHz
$CDCl_3$



0.95
0.95
2.89
1.28
1.05
2.70
3.0
2.5
2.0
1.5
1.0
0.5
0.0

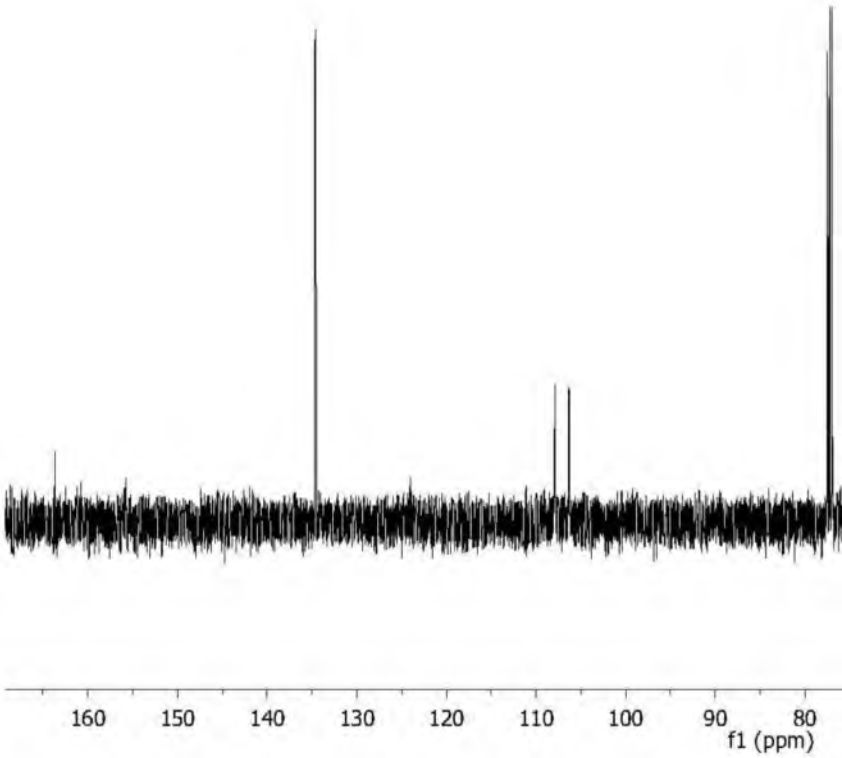

MeO2C
13C NMR
100 MHz
CDCl3
2.127
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

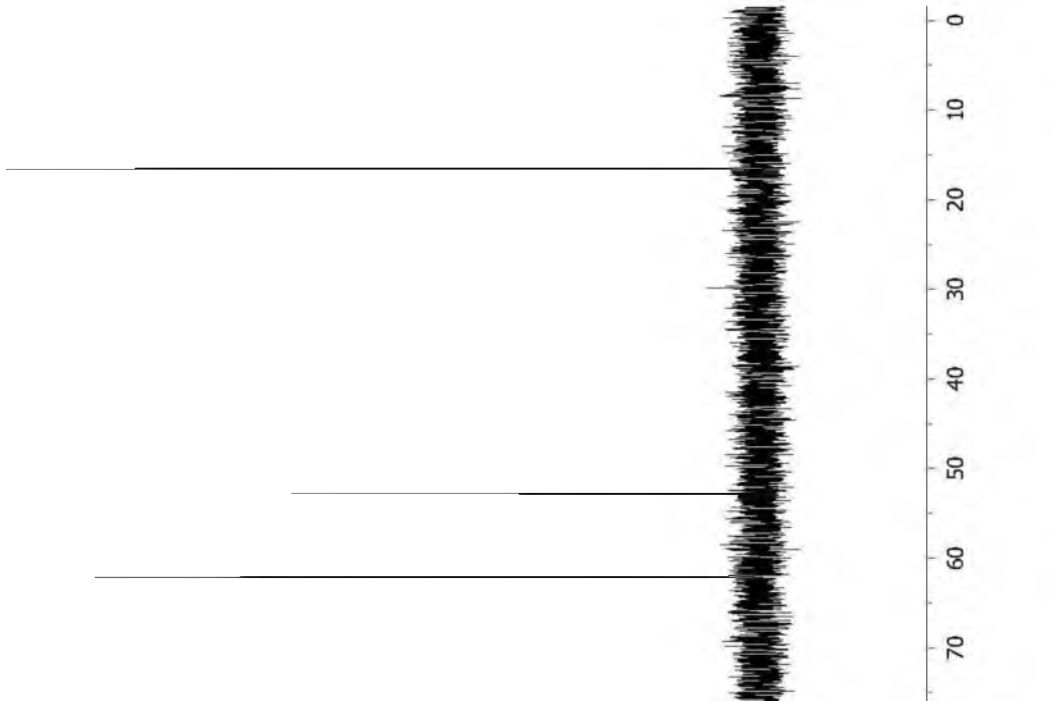

MeO2C
O
OEt
P
OEt
N2
3.4
1H NMR
500 MHz
CDCl3
0.72
0.65
3.92
3.00
6.49
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

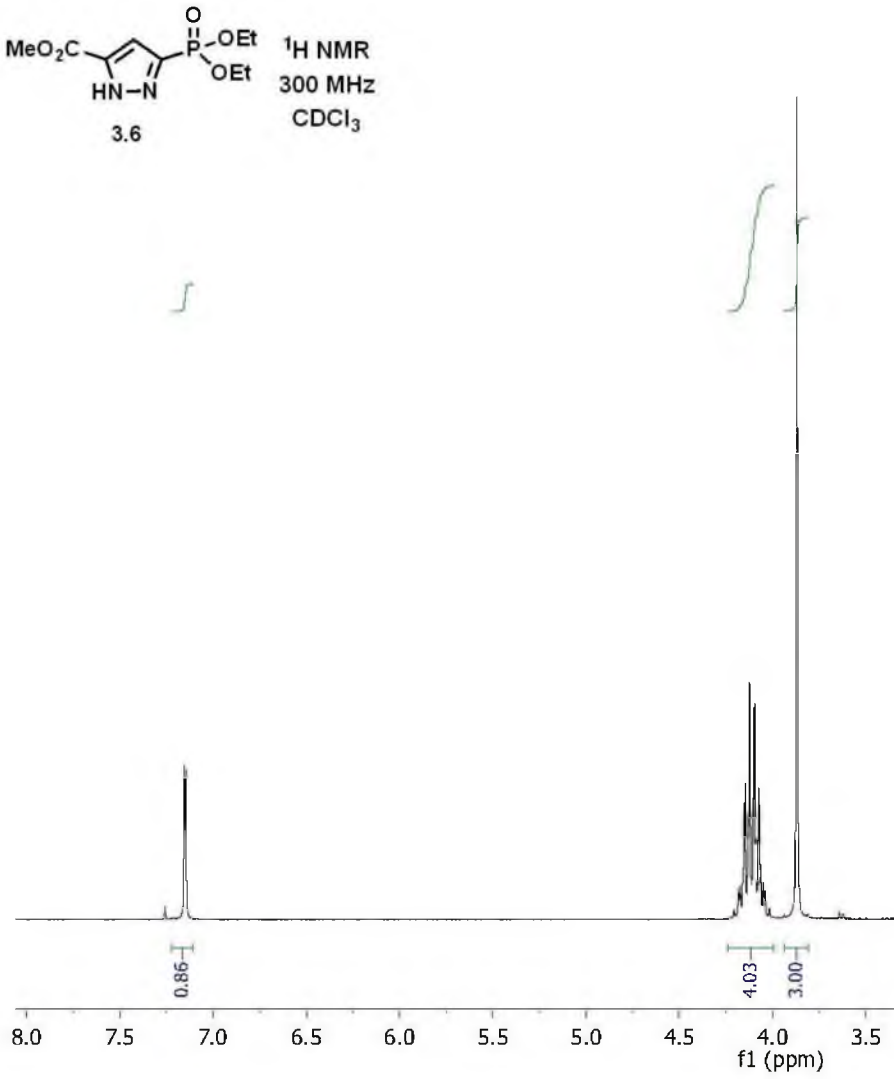


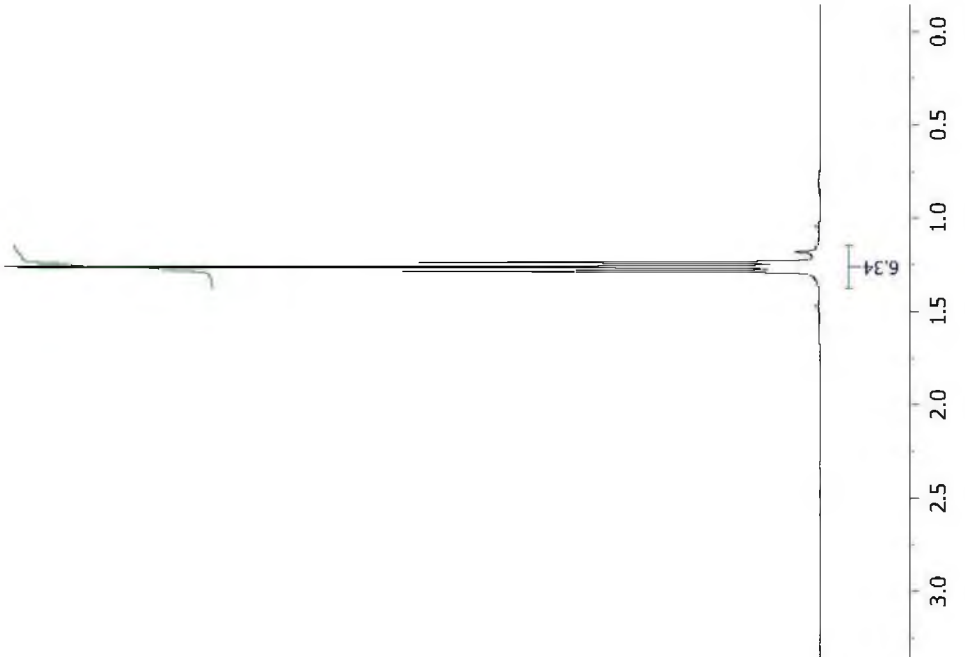
3.4

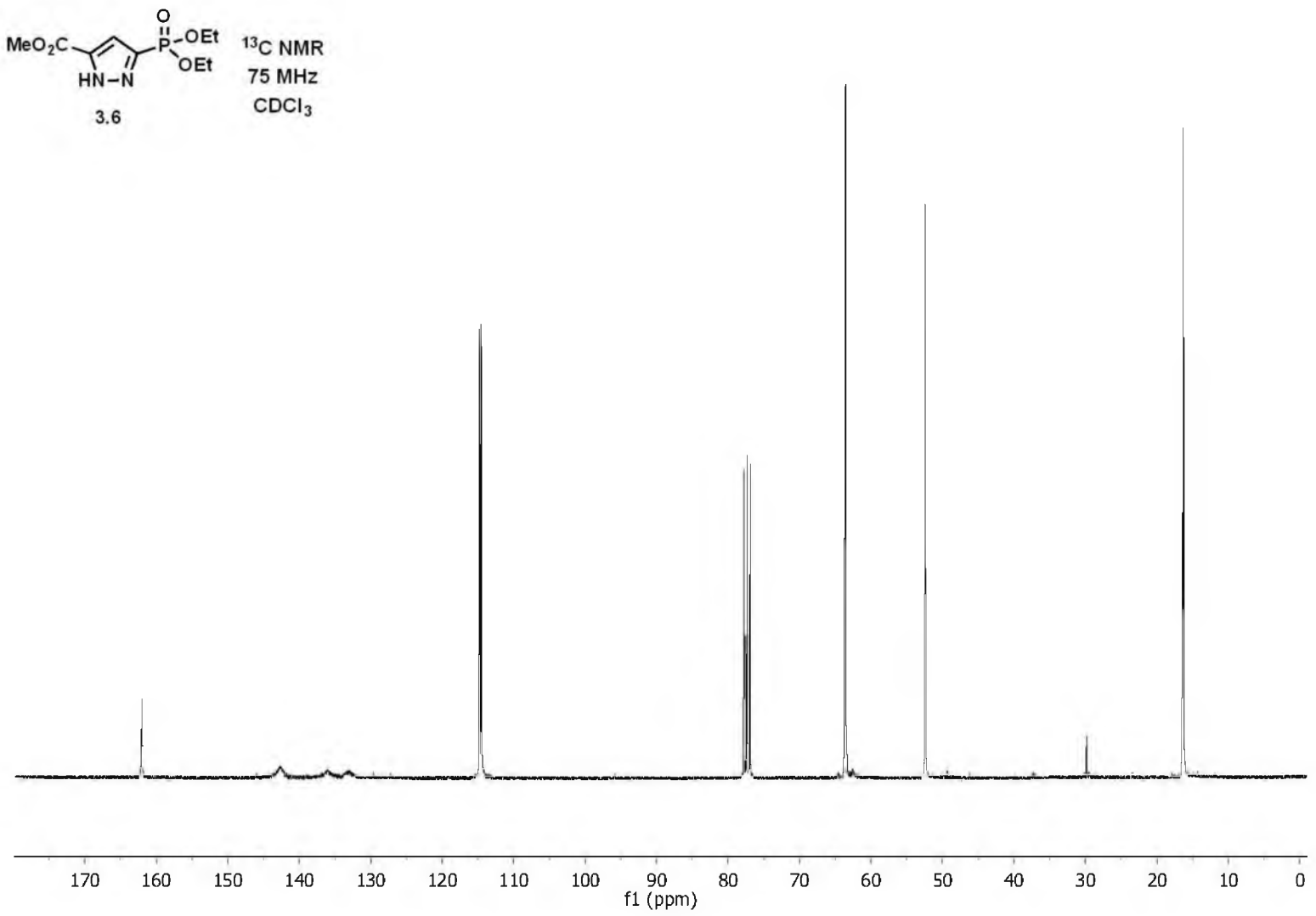
^{13}C NMR
125 MHz
$CDCl_3$

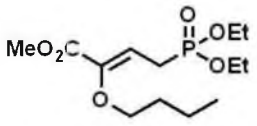



0
10
20
30
40
50
60
70


MeO2C
O
P
OEt
OEt
HN–N
3.6
1H NMR
300 MHz
CDCl3
0.86
4.03
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

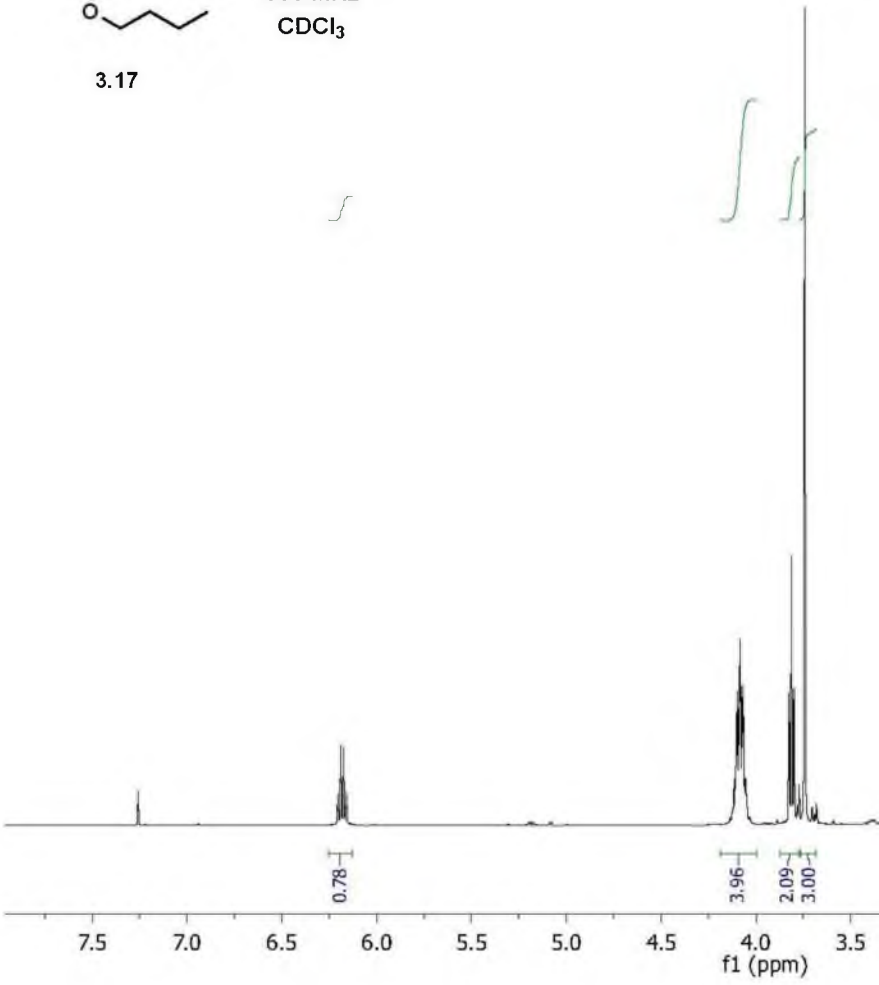

6.34
0.0
0.5
1.0
1.5
2.0
2.5
3.0

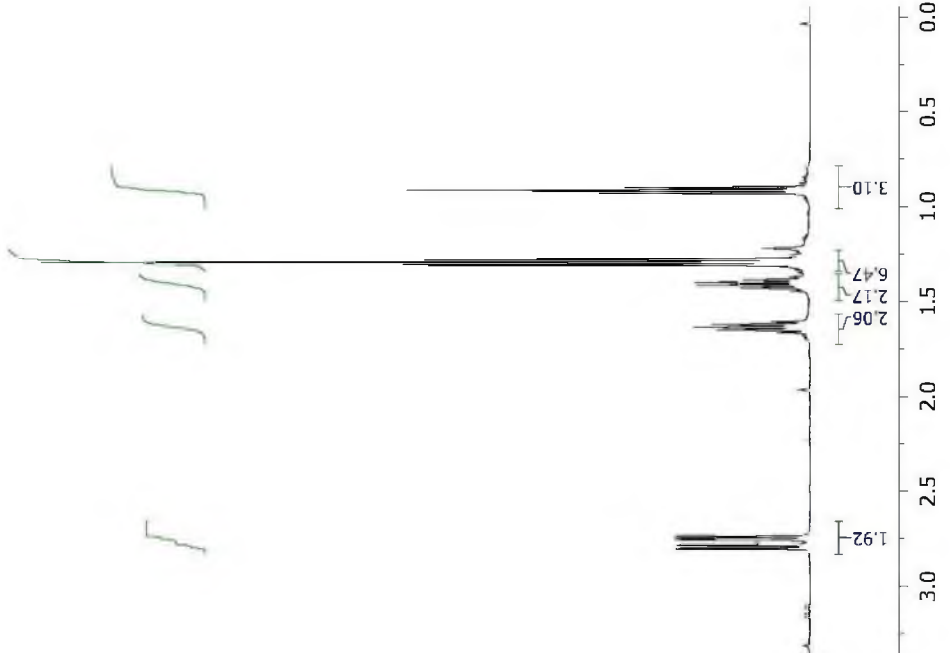

MeO2C
O
P
OEt
OEt
HN–N
3.6
13C NMR
75 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

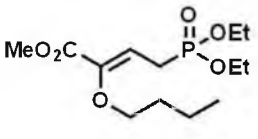


3.17

^{1}H NMR
500 MHz
$CDCl_3$

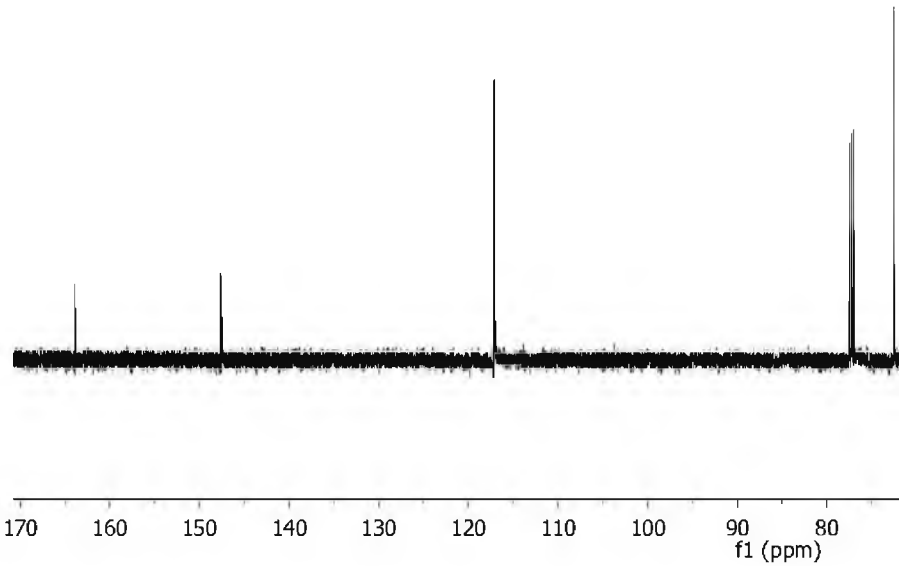


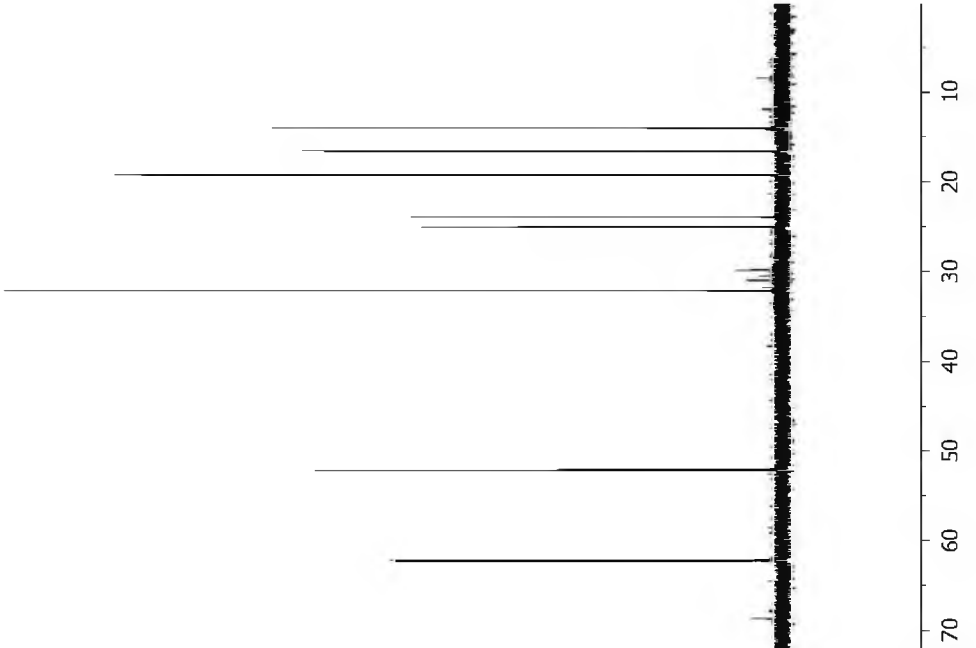

3.10
6.47
2.17
2.06
1.92
0.0
0.5
1.0
1.5
2.0
2.5
3.0

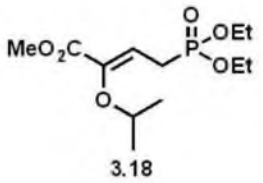


^{13}C NMR
125 MHz
$CDCl_3$

3.17

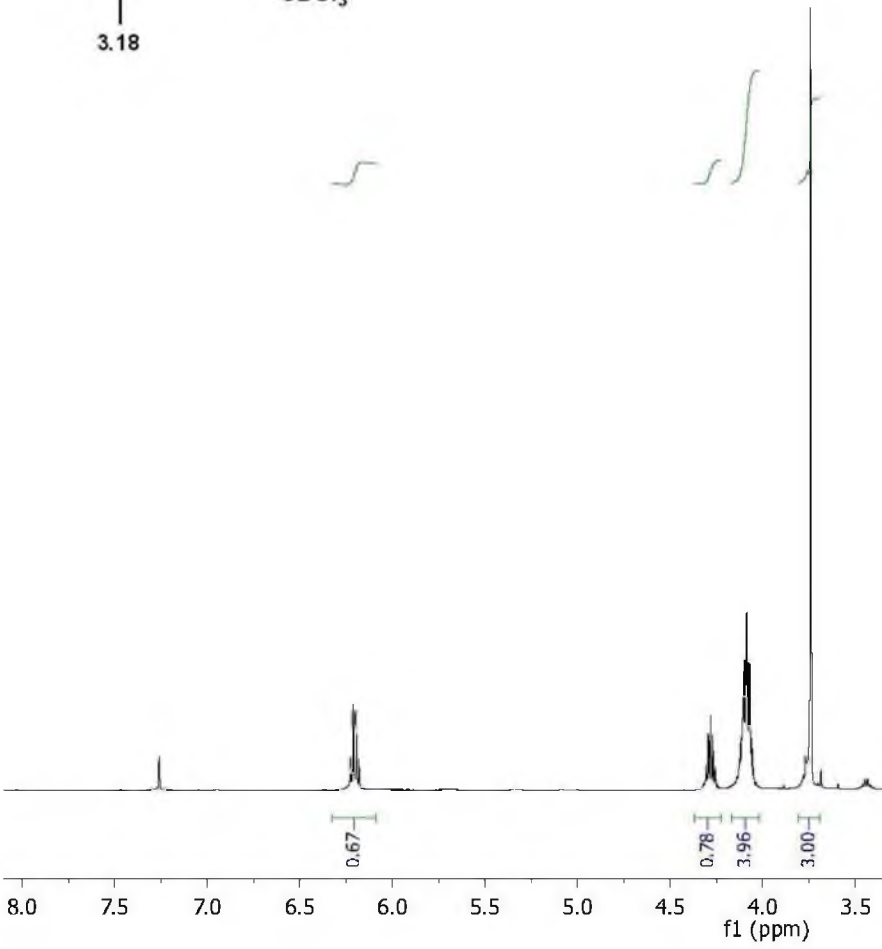


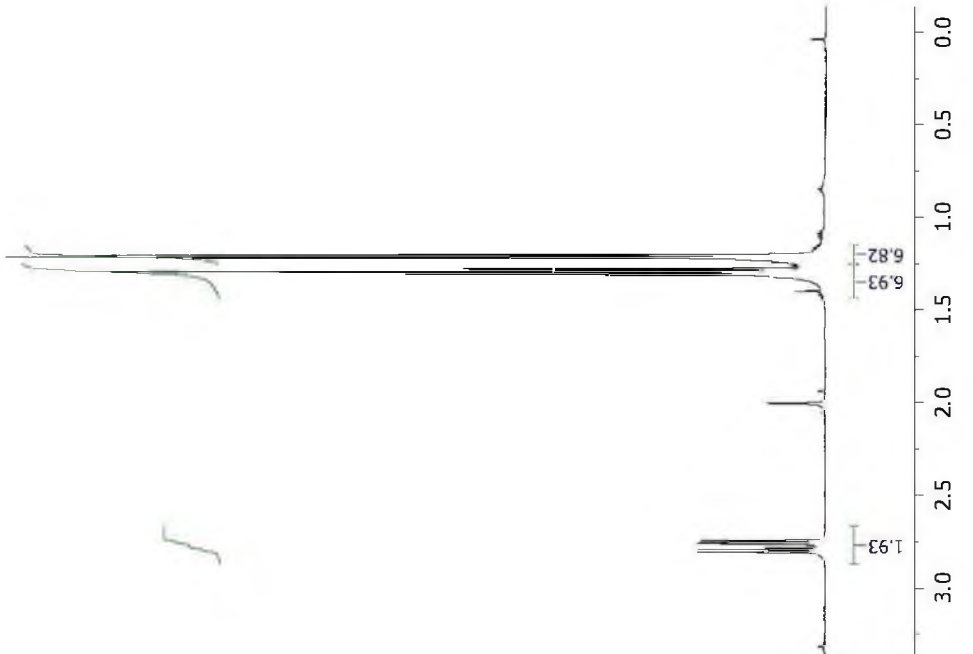

10
20
30
40
50
60
70

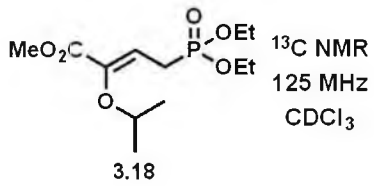


3.18

^{1}H NMR
500 MHz
$CDCl_3$

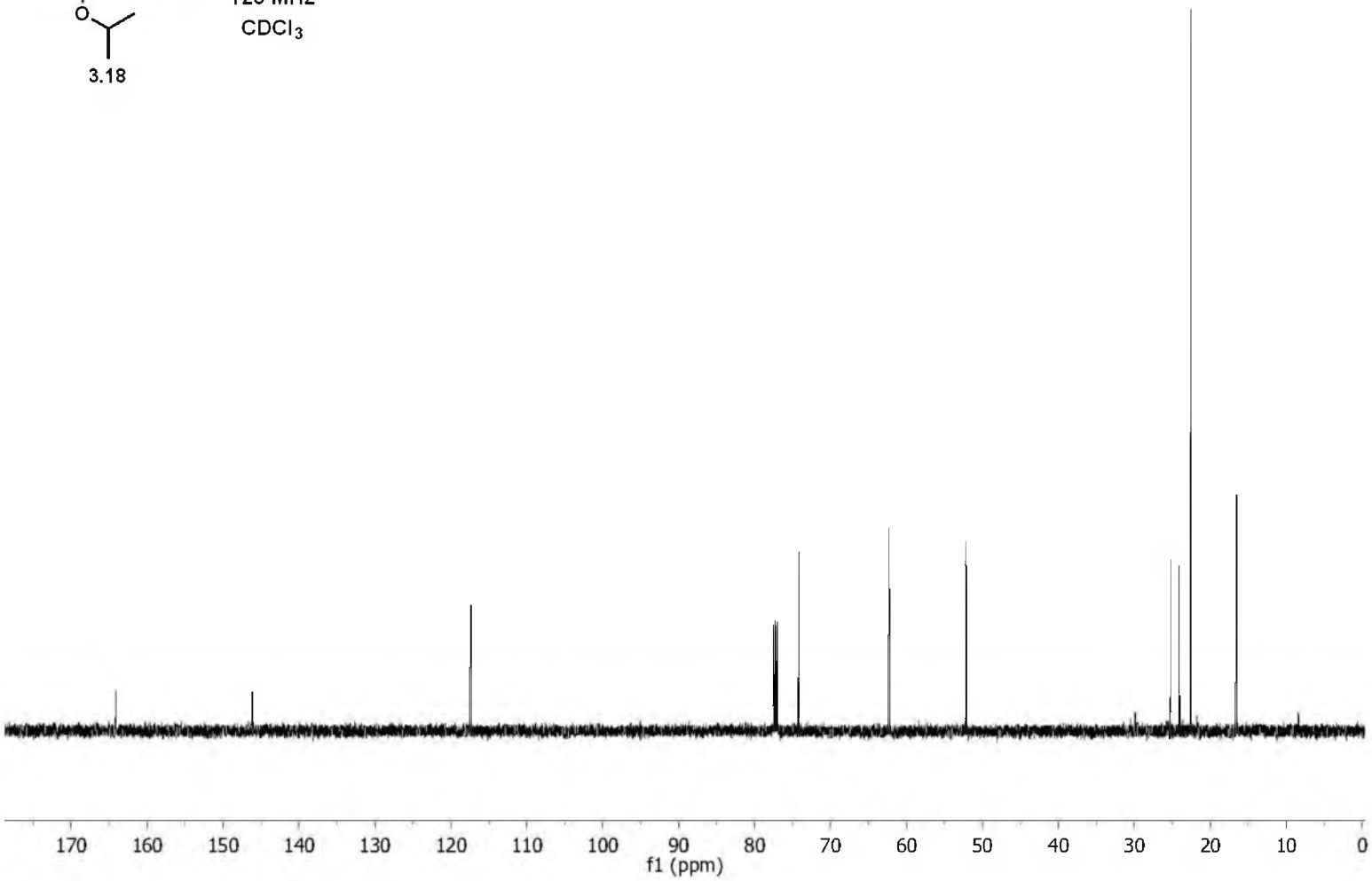


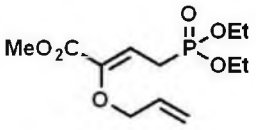

6.82
6.93
1.93
0.0
0.5
1.0
1.5
2.0
2.5
3.0



3.18

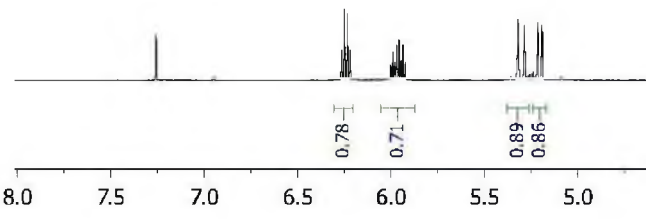
^{13}C NMR
125 MHz
$CDCl_3$

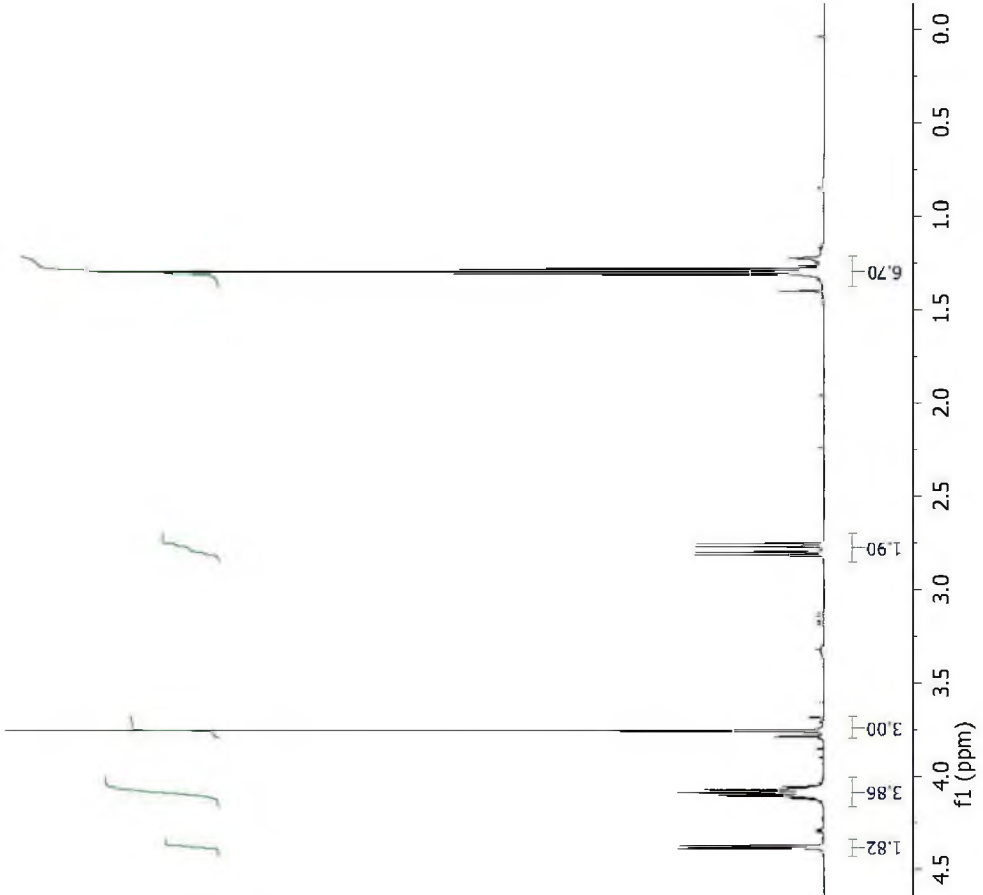


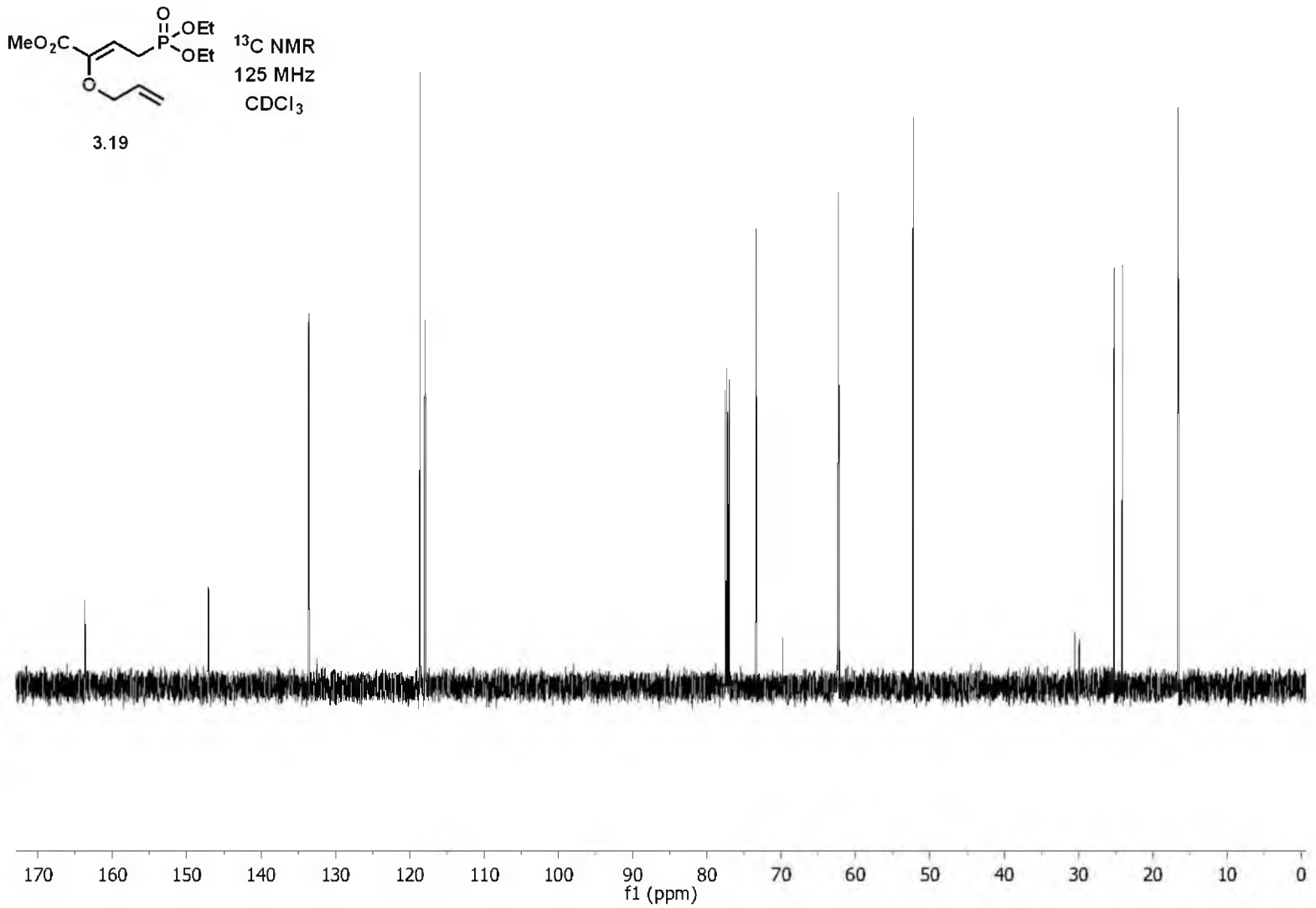


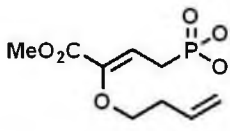
3.19

^{1}H NMR
500 MHz
$CDCl_3$



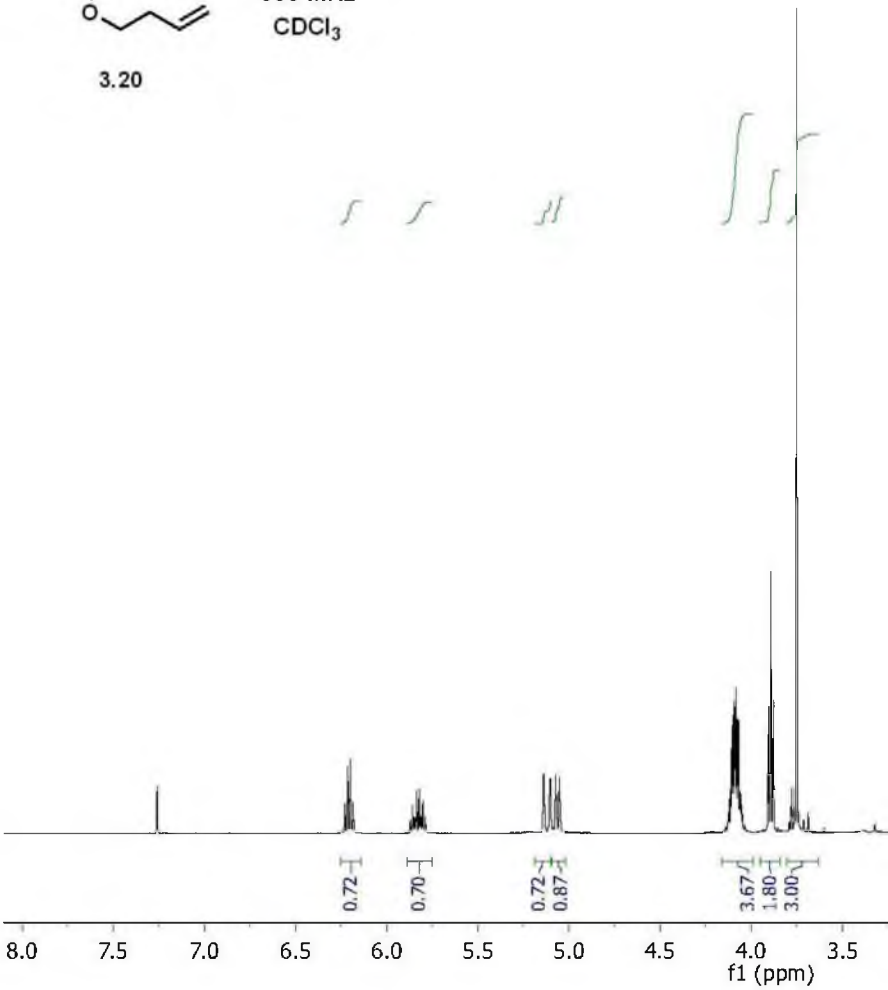

6.70
1.90
3.00
3.86
1.82
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

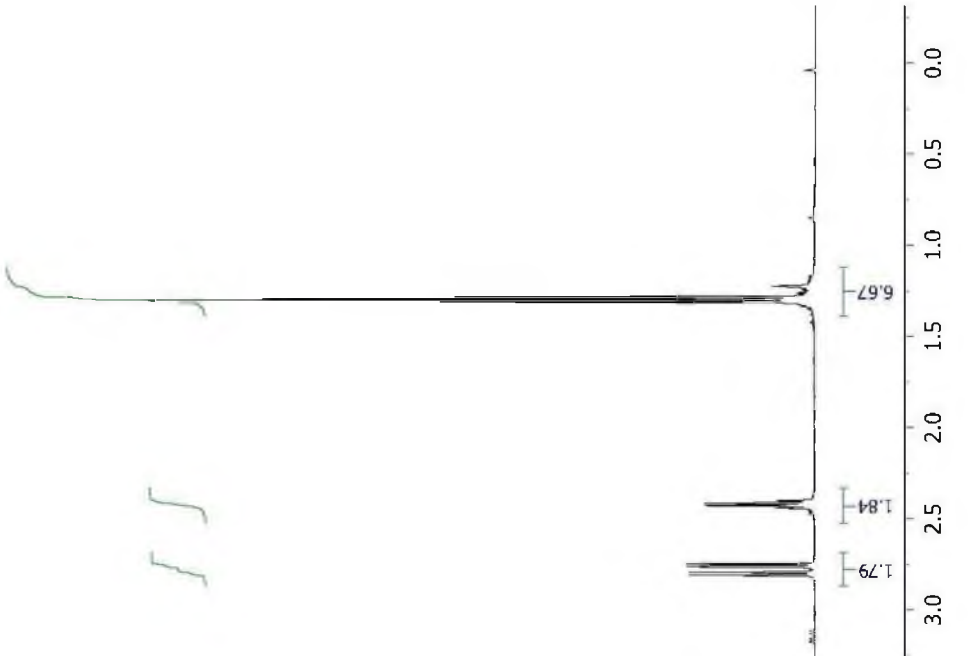

MeO2C
OEt
OEt
O
P
O
O
13C NMR
125 MHz
CDCl3
3.19
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

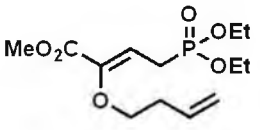


3.20

^{1}H NMR
500 MHz
$CDCl_3$

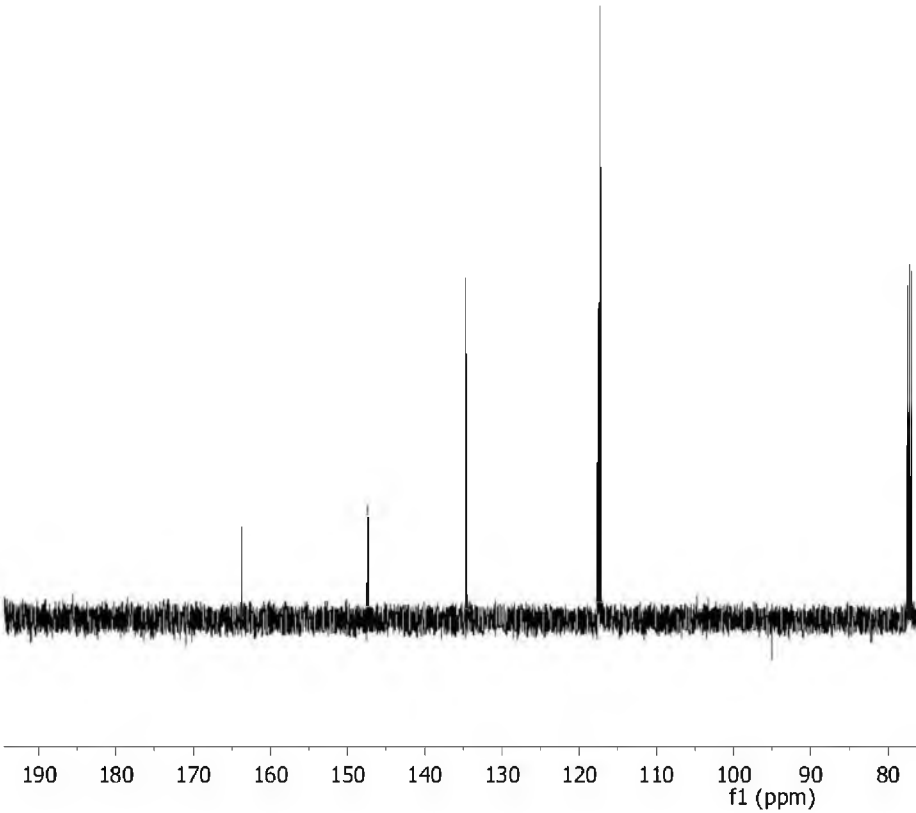


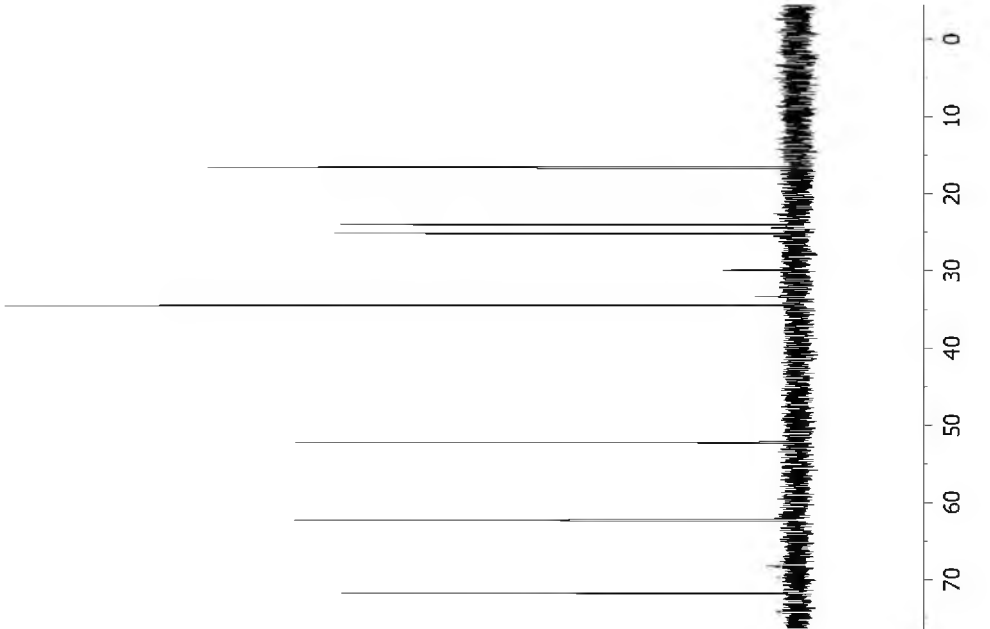

6.67
1.84
1.79
3.0
2.5
2.0
1.5
1.0
0.5
0.0

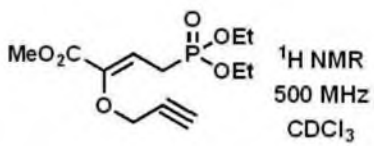


^{13}C NMR
125 MHz
$CDCl_3$

3.20

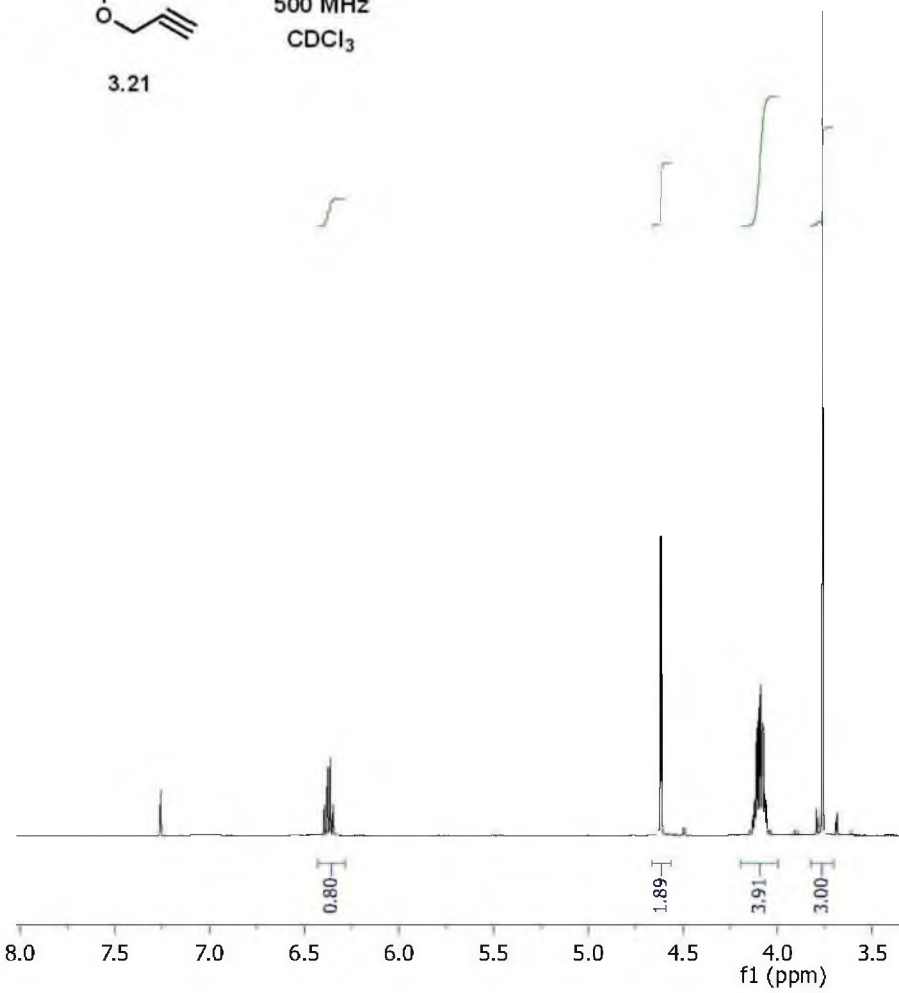


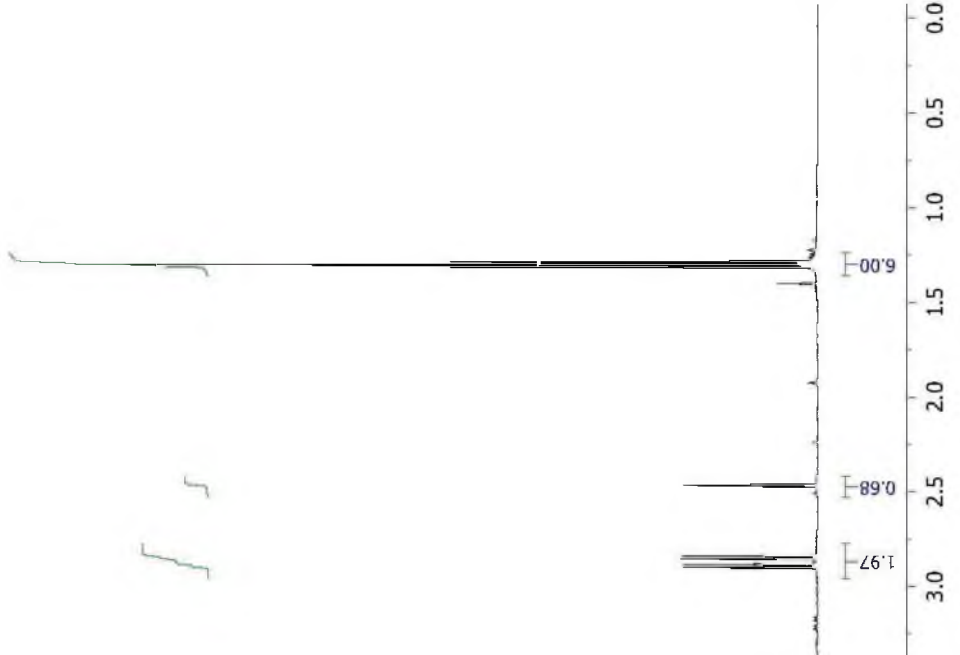

0
10
20
30
40
50
60
70

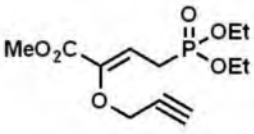


3.21

^{1}H NMR
500 MHz
$CDCl_3$

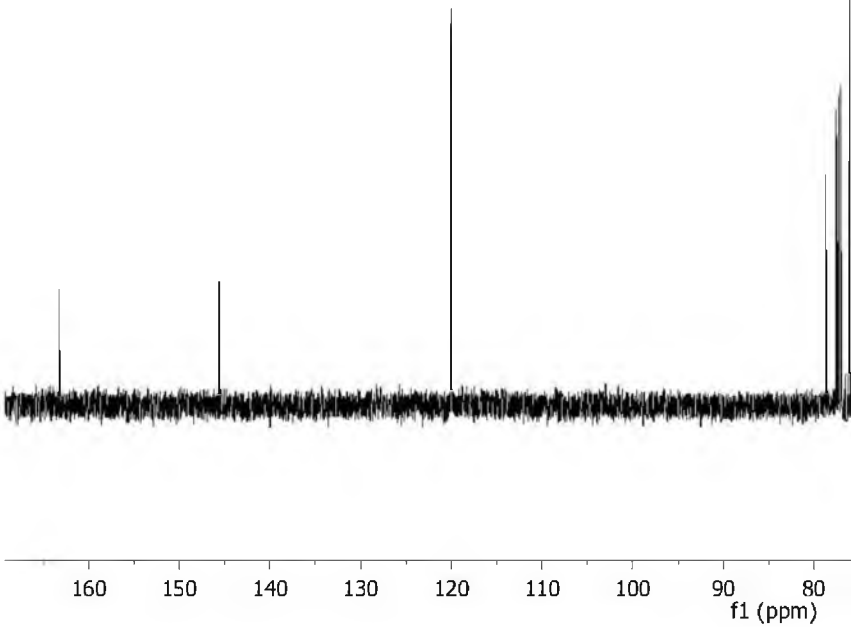


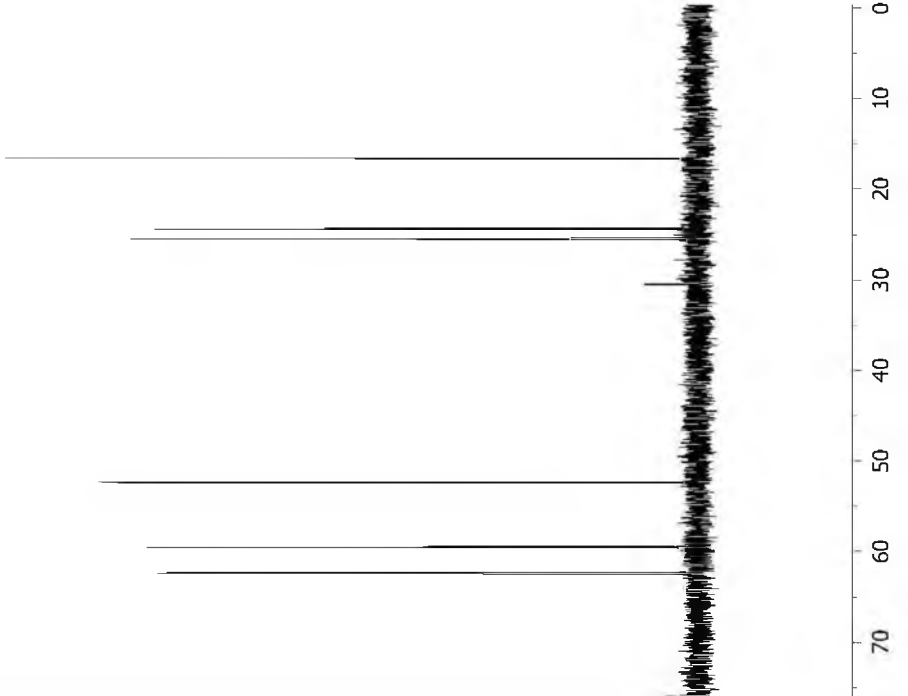

6.00
0.68
1.97
0.0
0.5
1.0
1.5
2.0
2.5
3.0

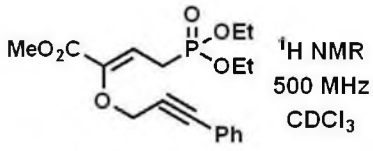


^{13}C NMR
125 MHz
$CDCl_3$

3.21

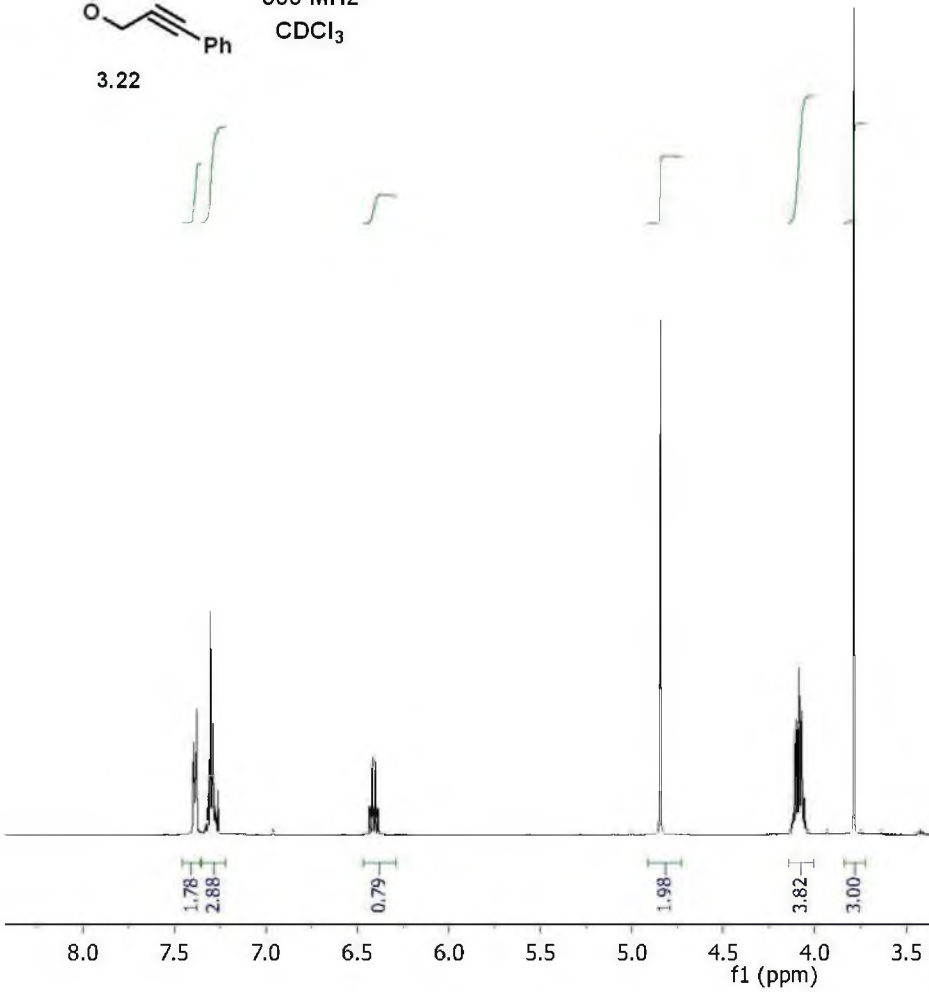


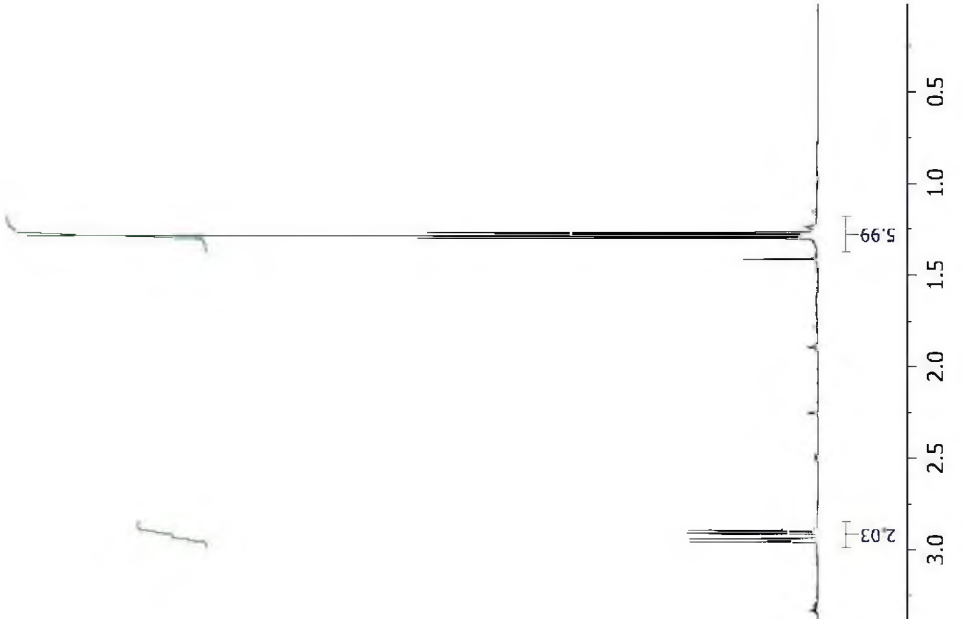

0
10
20
30
40
50
60
70

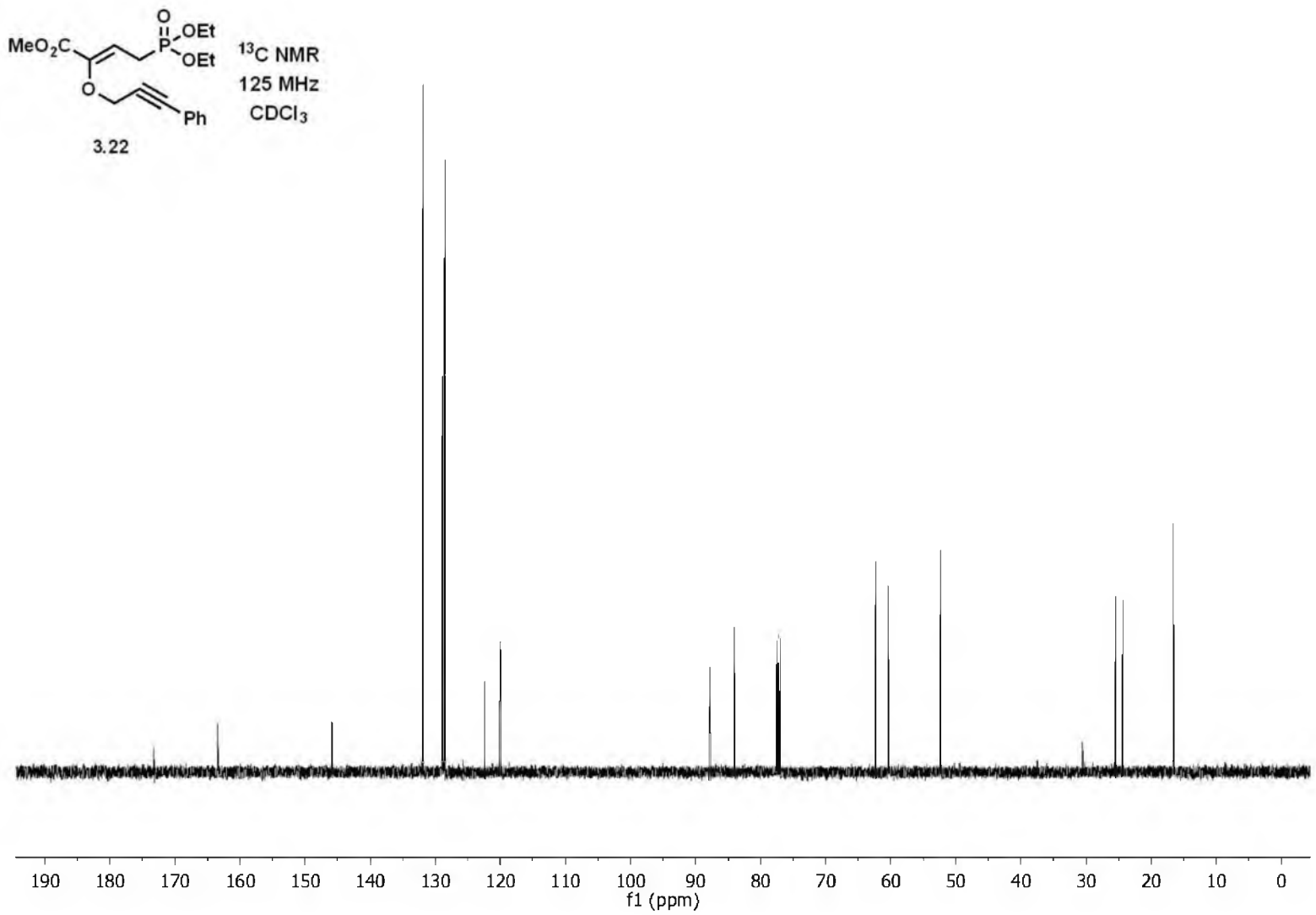


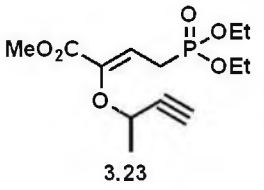
3.22

^{1}H NMR
500 MHz
$CDCl_3$



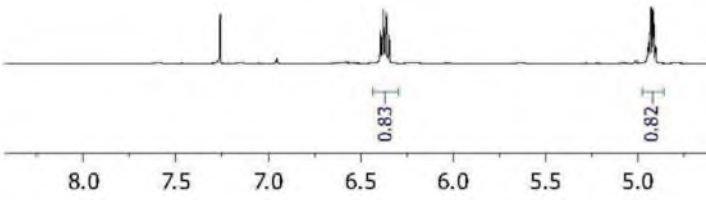

5.99
2.03
3.0
2.5
2.0
1.5
1.0
0.5

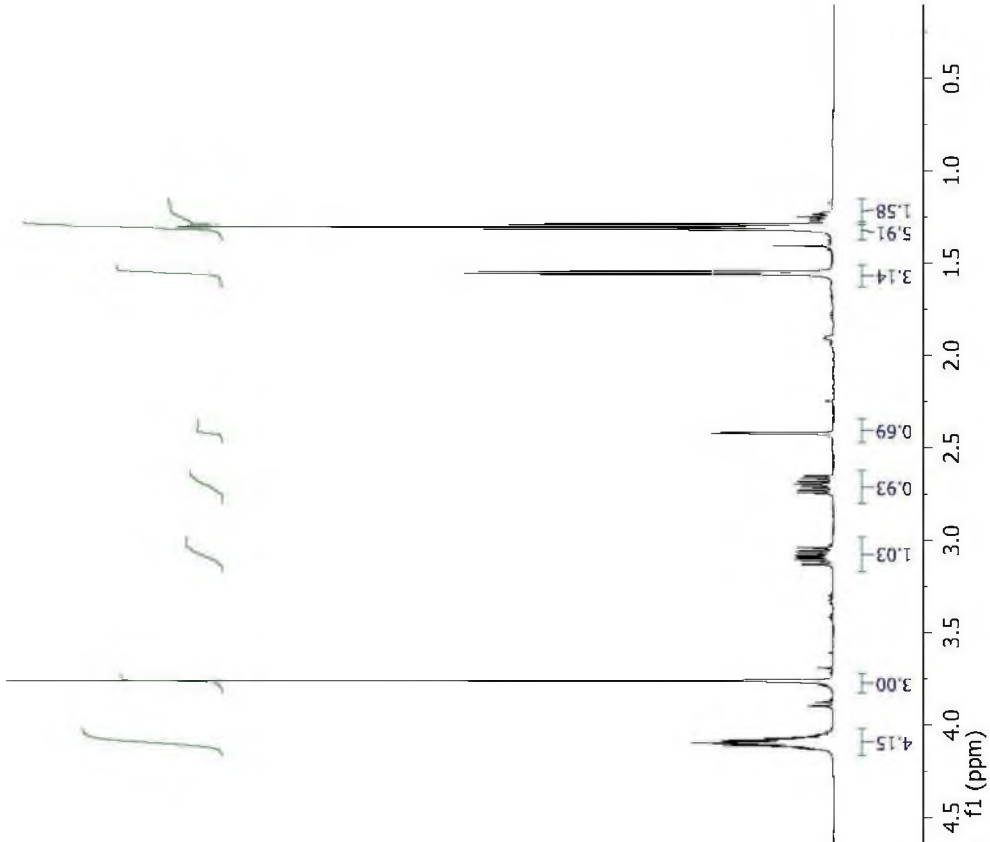

MeO2C
O
P
OEt
OEt
O
Ph
3.22
13C NMR
125 MHz
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

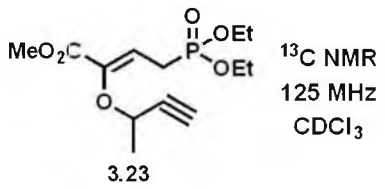


3.23

^{1}H NMR
500 MHz
$CDCl_3$

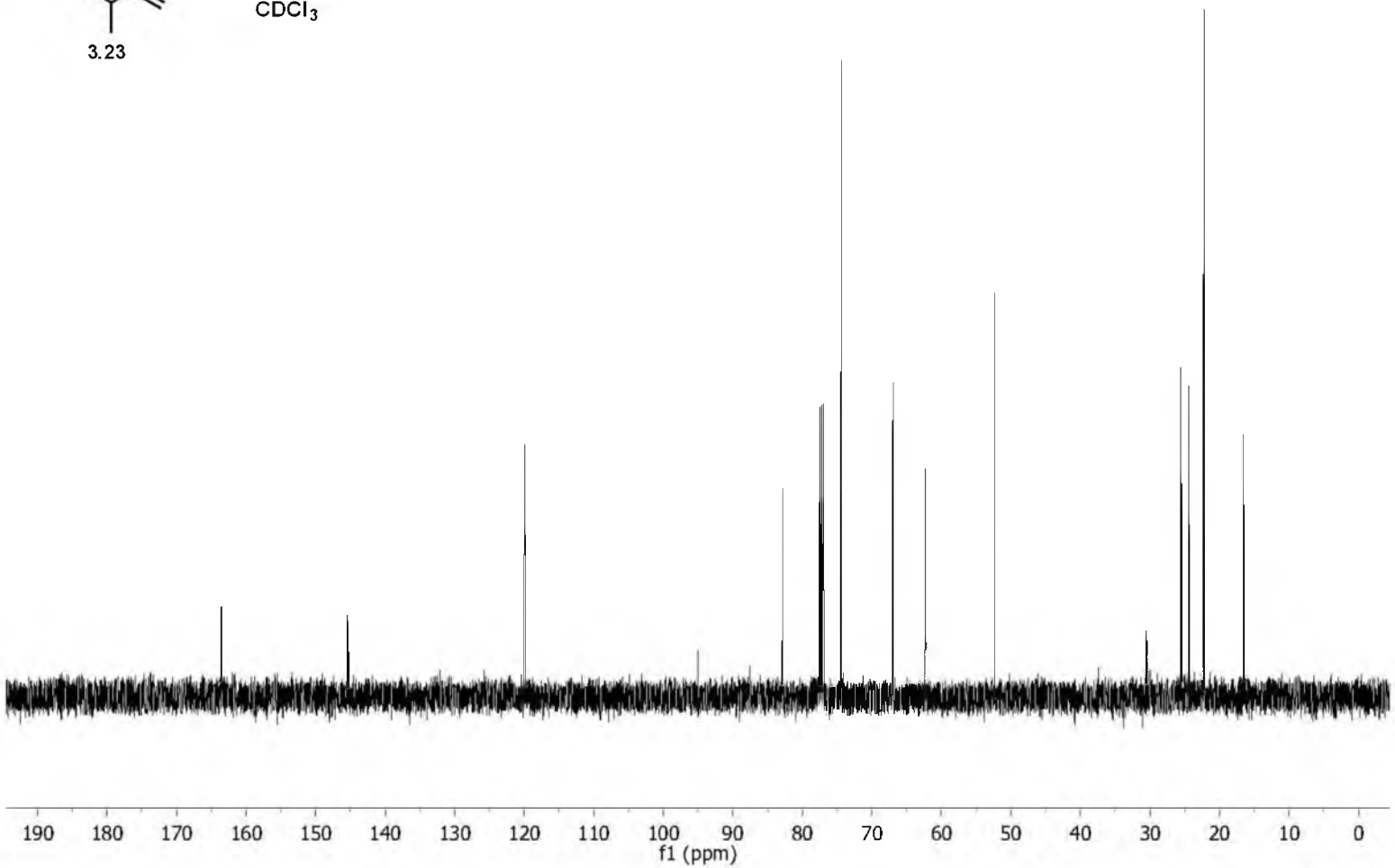


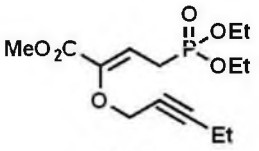

4.15
3.00
1.03
0.93
0.69
3.14
5.91
1.58
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



3.23

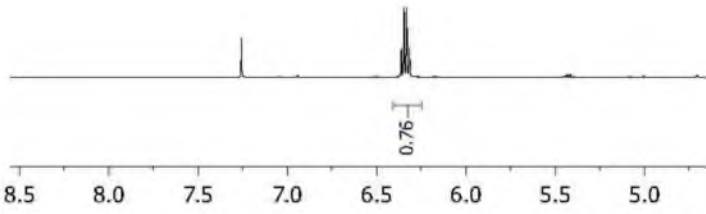
^{13}C NMR
125 MHz
$CDCl_3$

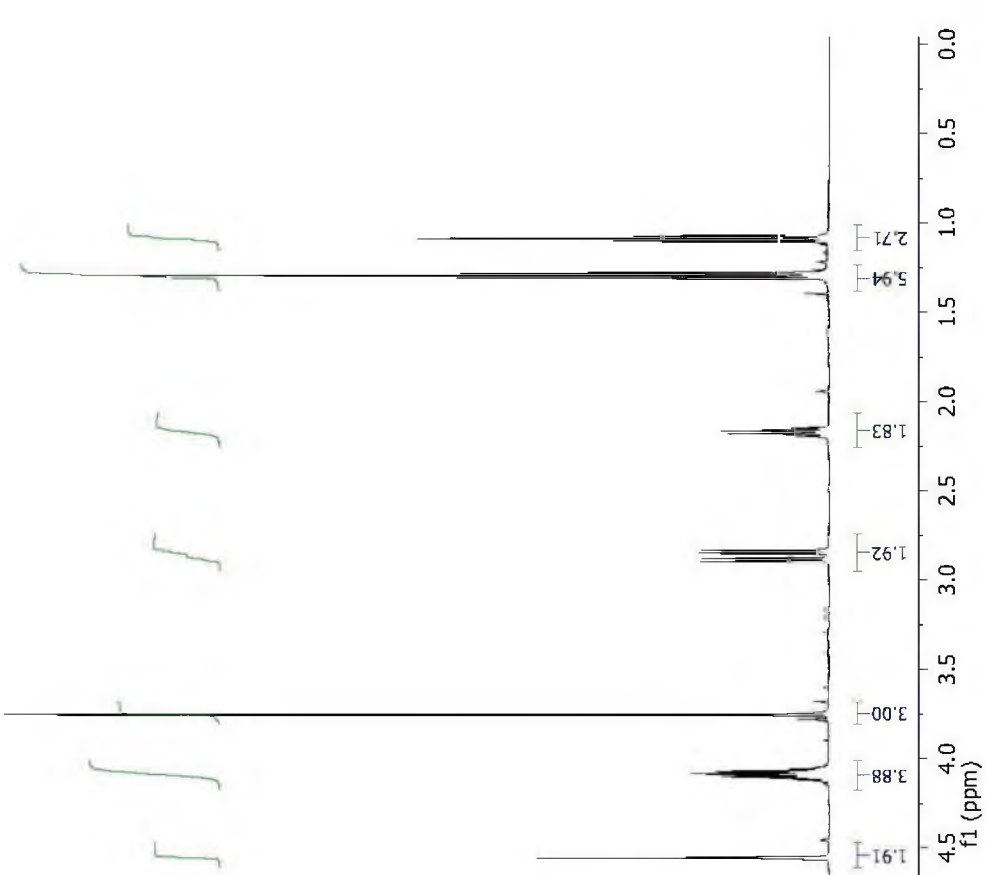


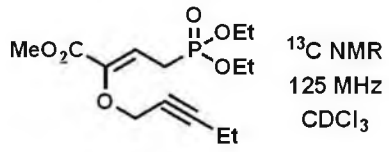


3.24

^{1}H NMR
500 MHz
$CDCl_3$

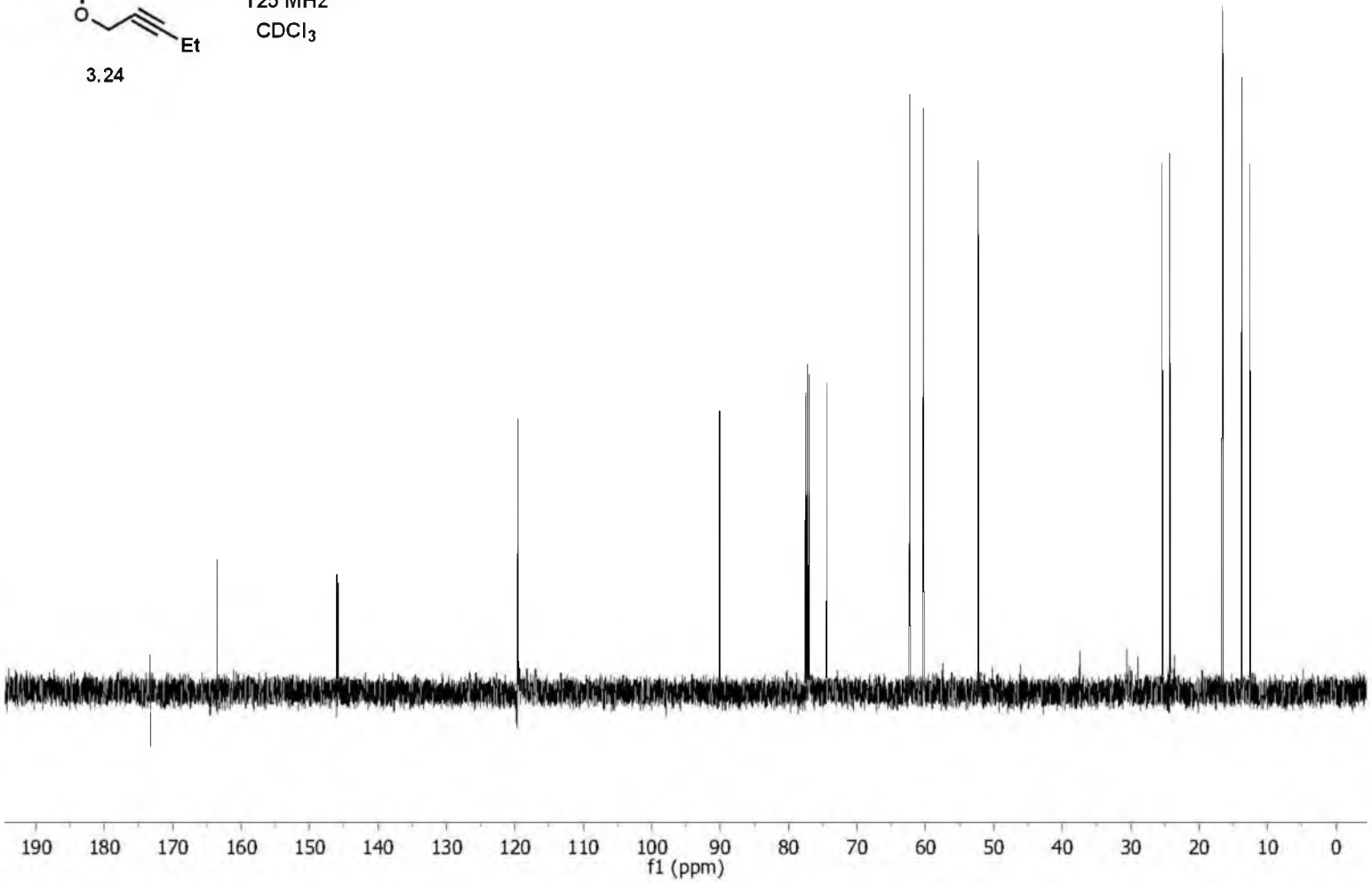


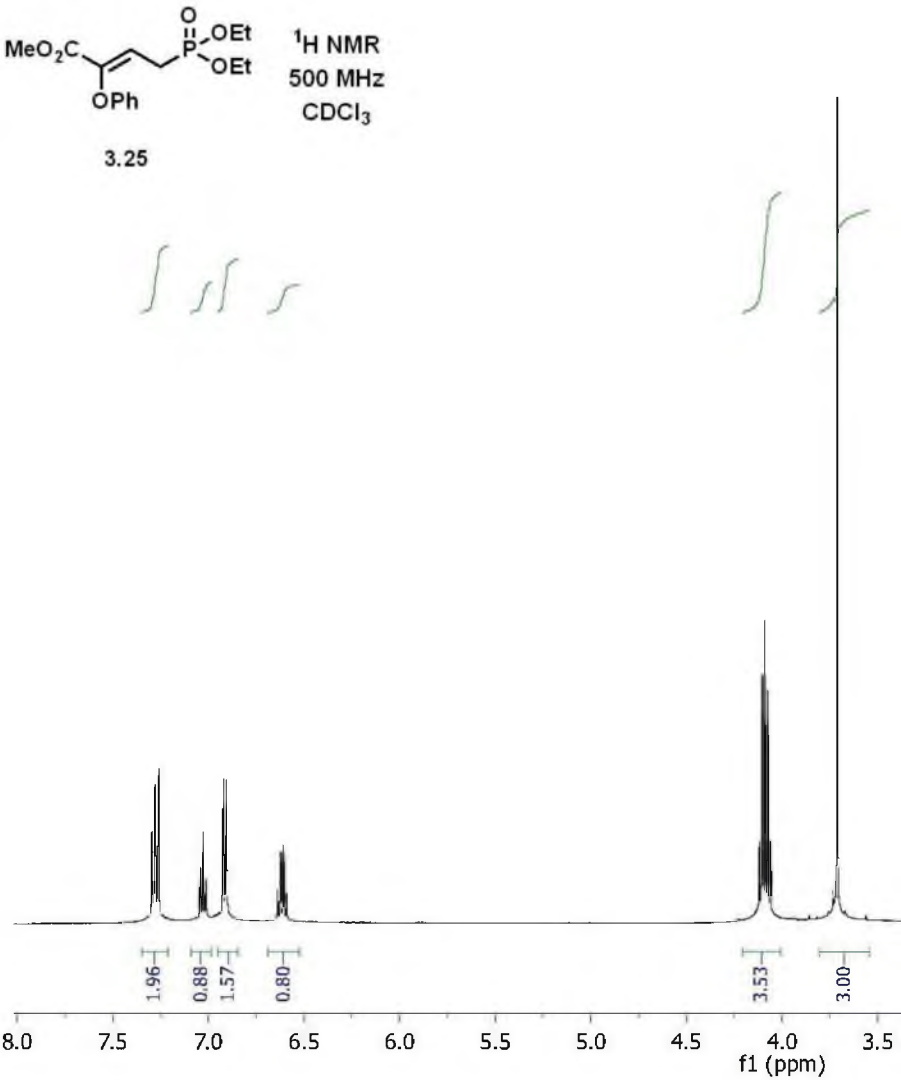

1.91
3.88
3.00
1.92
1.83
5.94
2.71
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

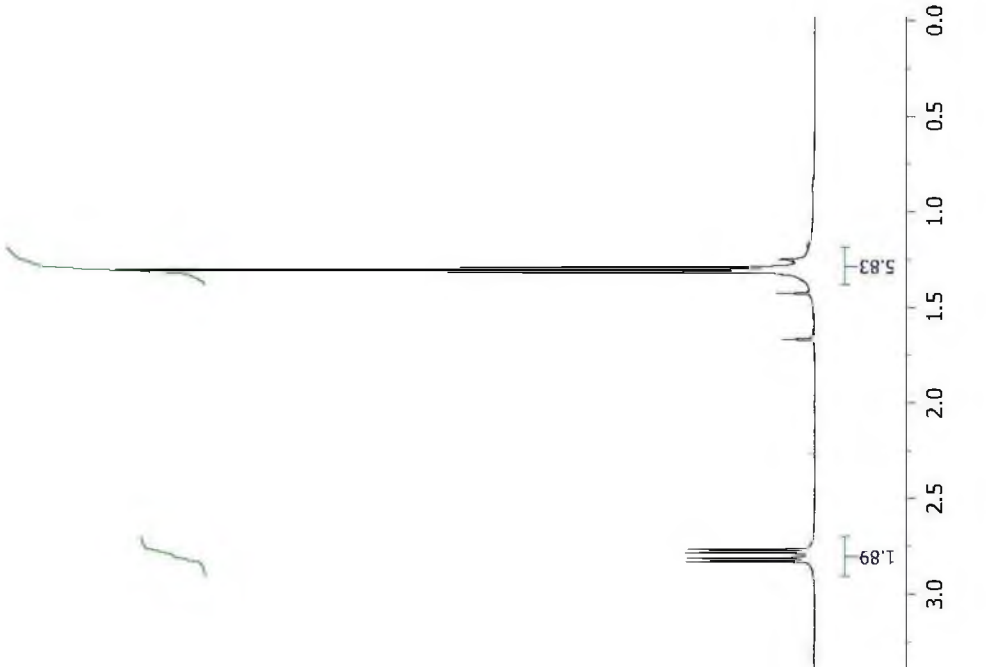


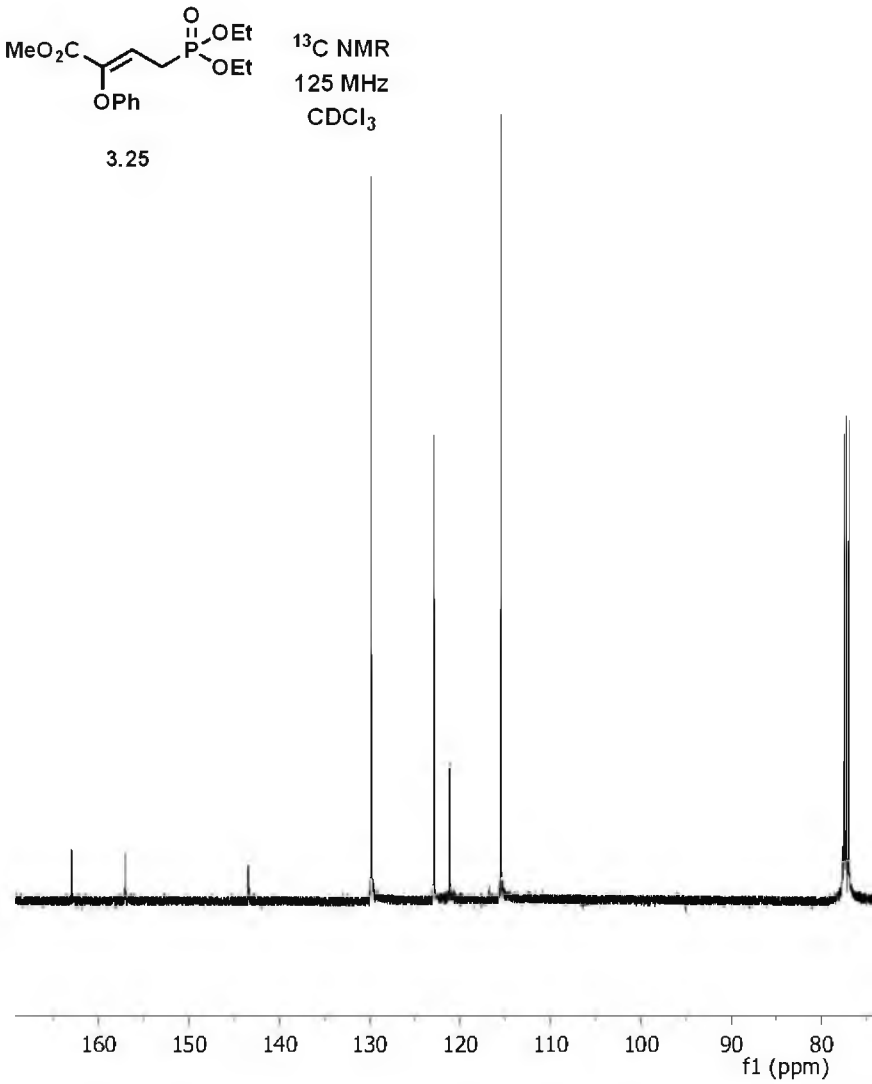
3.24

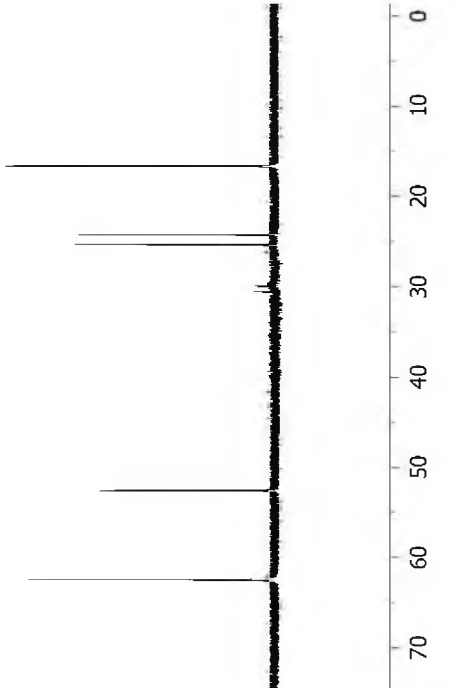
^{13}C NMR
125 MHz
$CDCl_3$

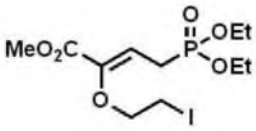



MeO2C
OPh
O
OEt
OEt
3.25
1H NMR
500 MHz
CDCl3
1.96
0.88
1.57
0.80
3.53
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)


5.83
1.89
0.0
0.5
1.0
1.5
2.0
2.5
3.0

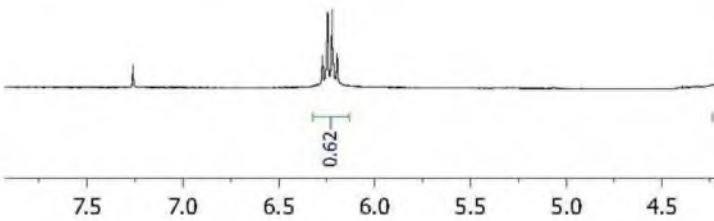

MeO2C
OPh
O
OEt
OEt
3.25
13C NMR
125 MHz
CDCl3
160
150
140
130
120
110
100
90
80
f1 (ppm)

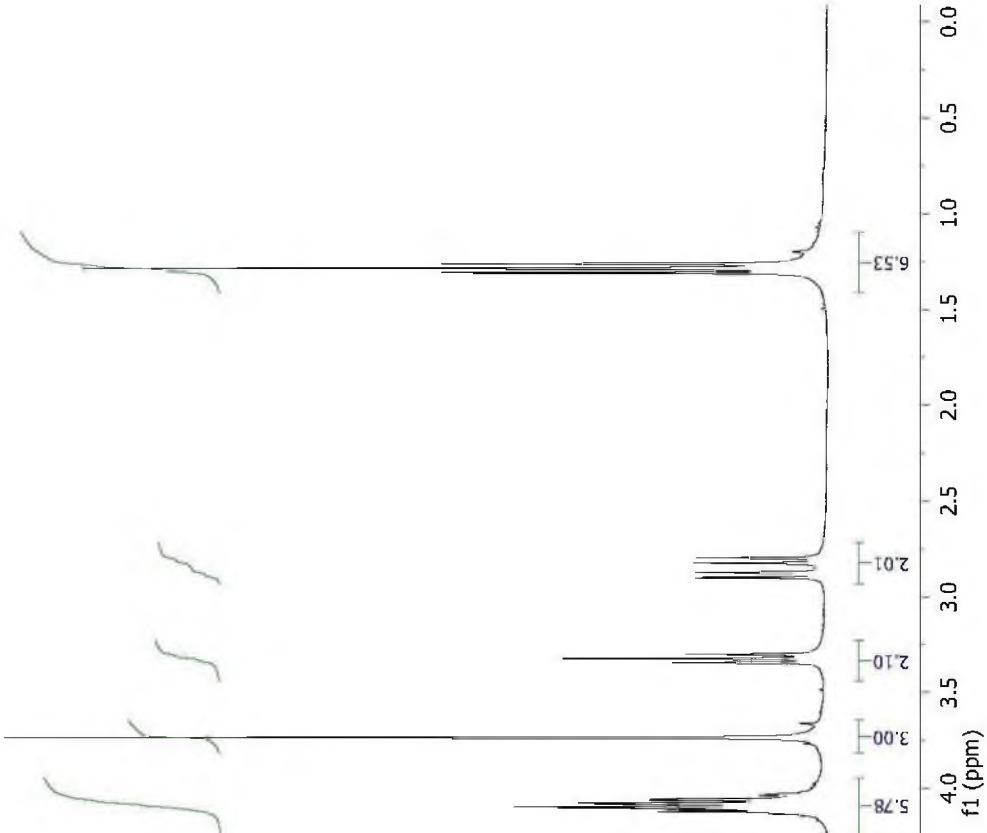

0
10
20
30
40
50
60
70

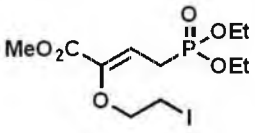


3.26

^{1}H NMR
500 MHz
$CDCl_3$

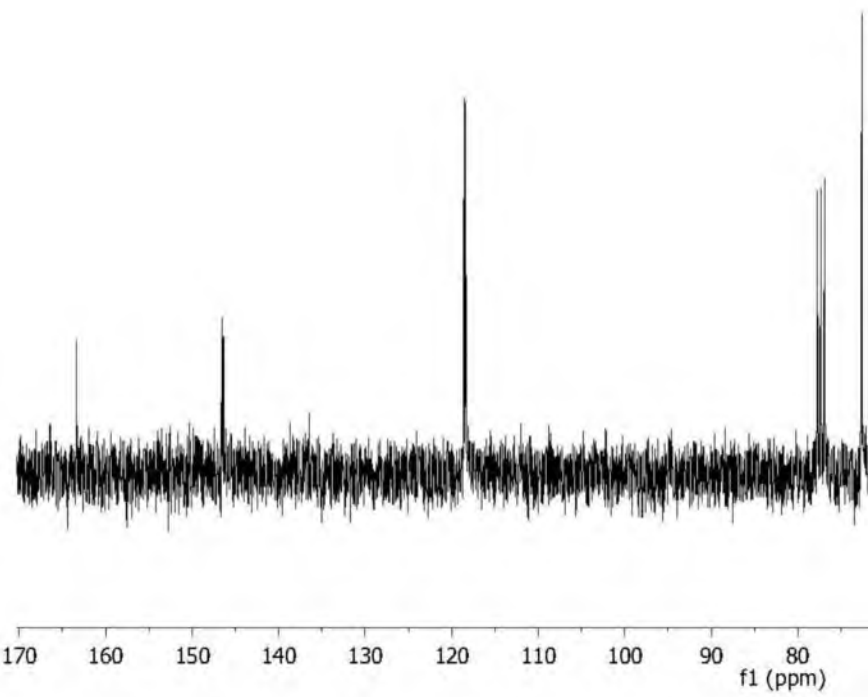


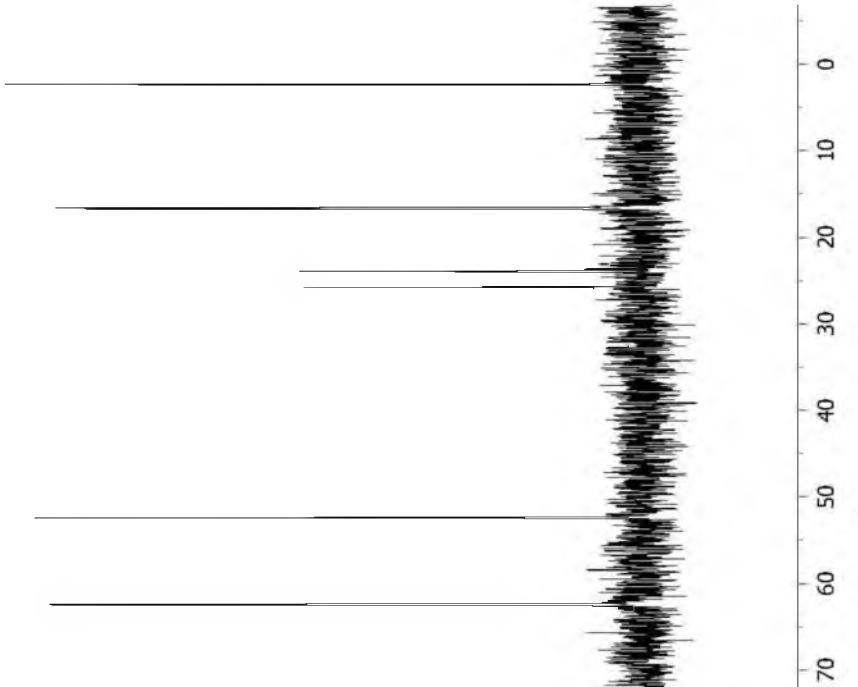

6.53
2.01
2.10
3.00
5.78
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

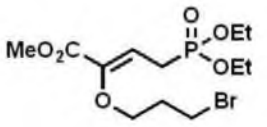


3.26

^{13}C NMR
125 MHz
$CDCl_3$

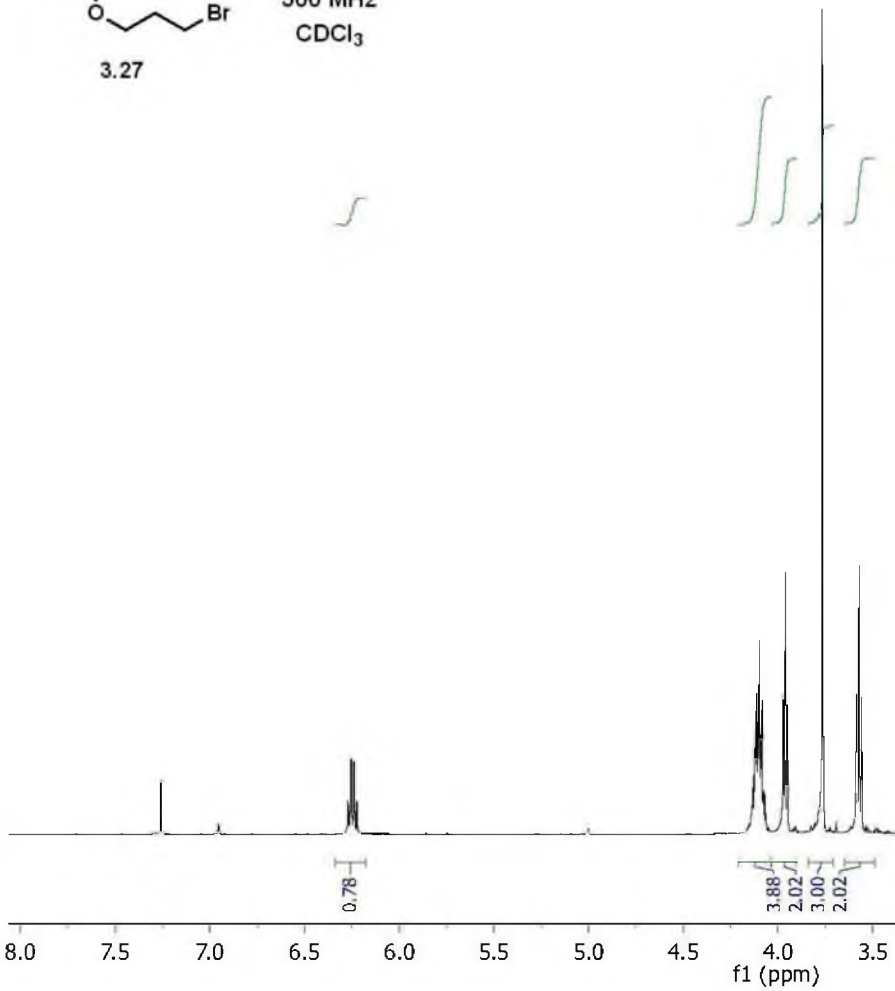


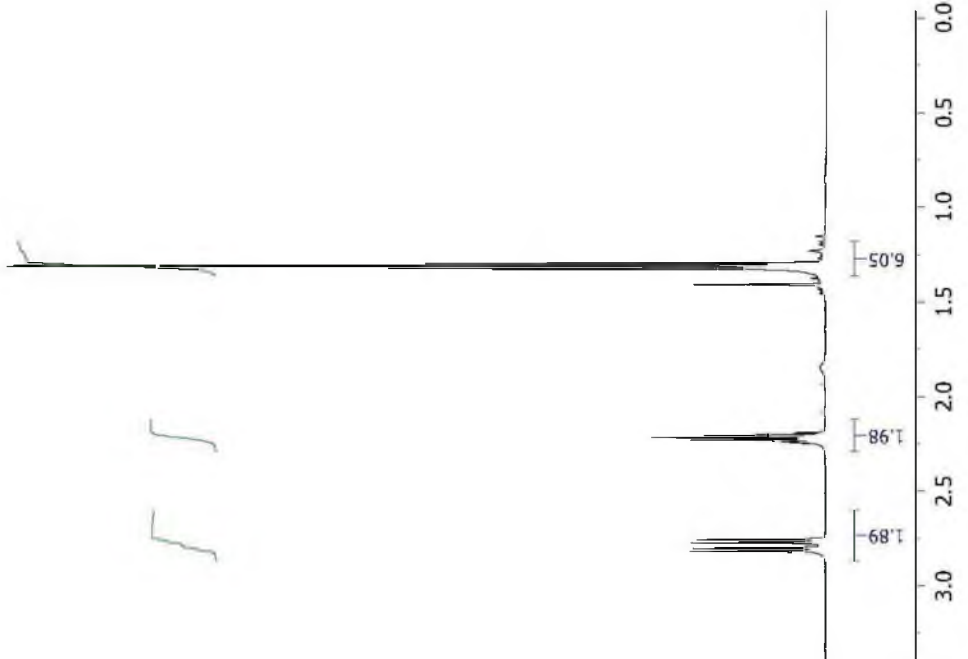

0
10
20
30
40
50
60
70

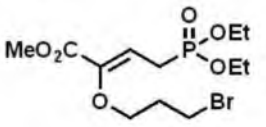


3.27

^{1}H NMR
500 MHz
$CDCl_3$

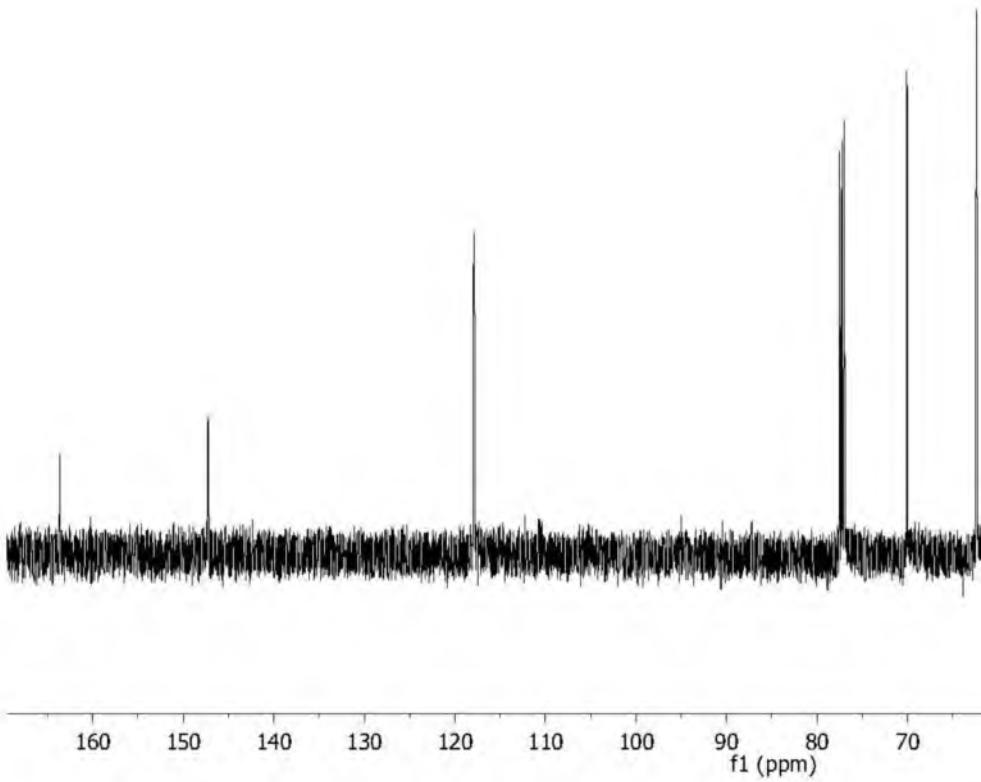


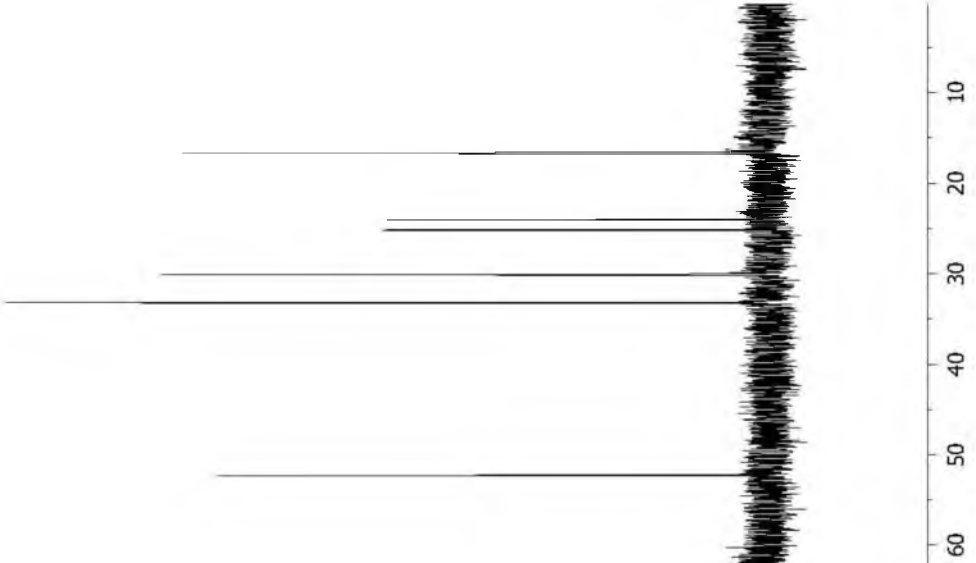

6,05
1,98
1,89
0.0
0.5
1.0
1.5
2.0
2.5
3.0

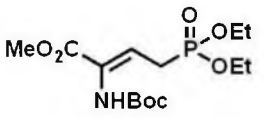


3.27

^{13}C NMR
125 MHz
$CDCl_3$

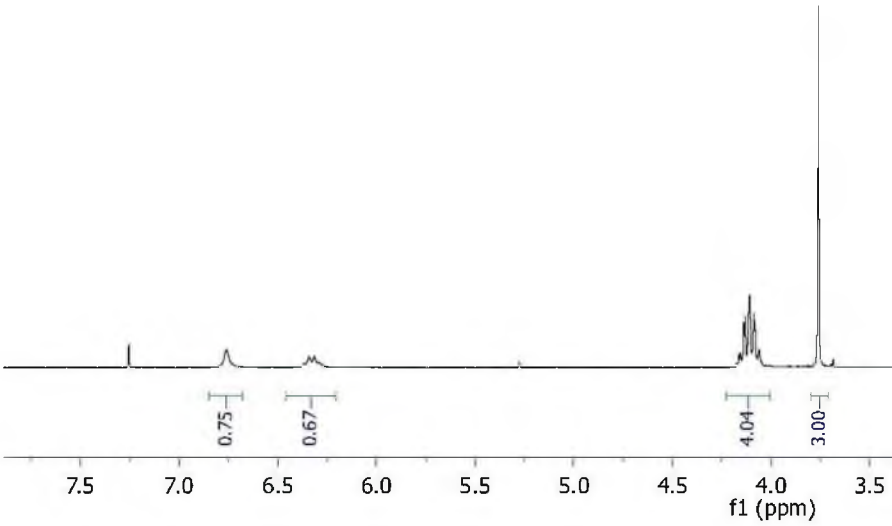


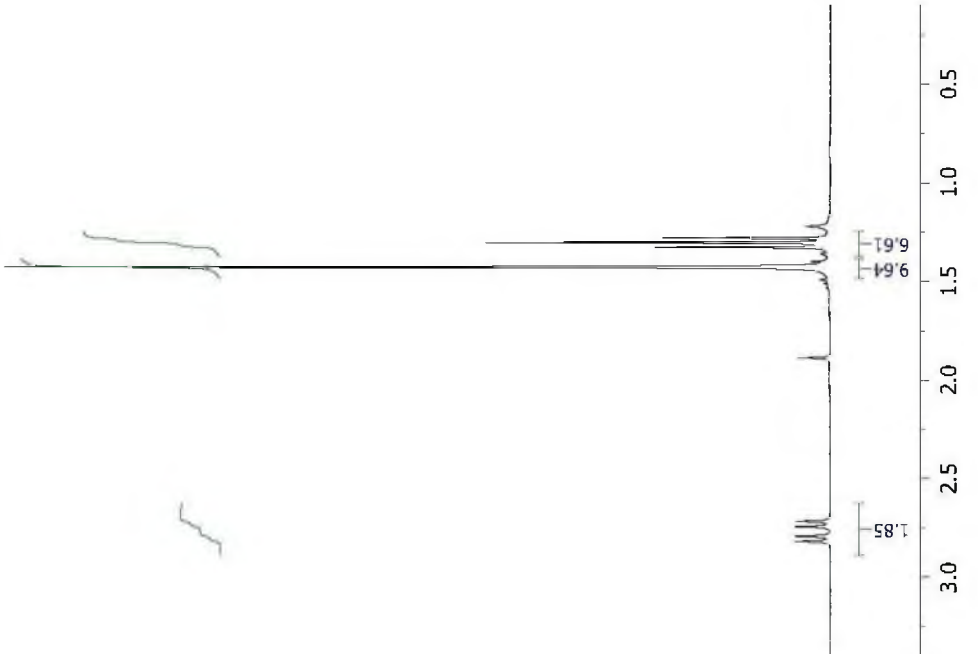

10
20
30
40
50
60

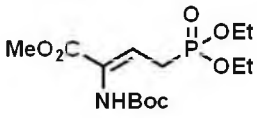


3.31

^{1}H NMR
300 MHz
$CDCl_3$

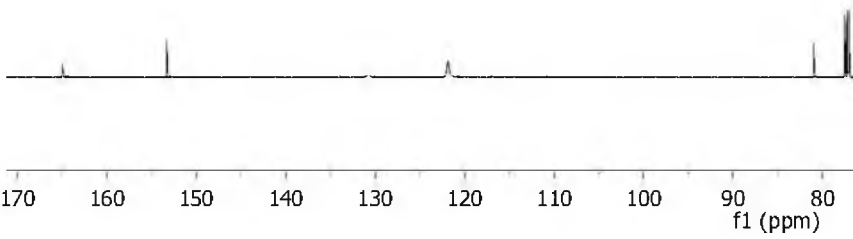


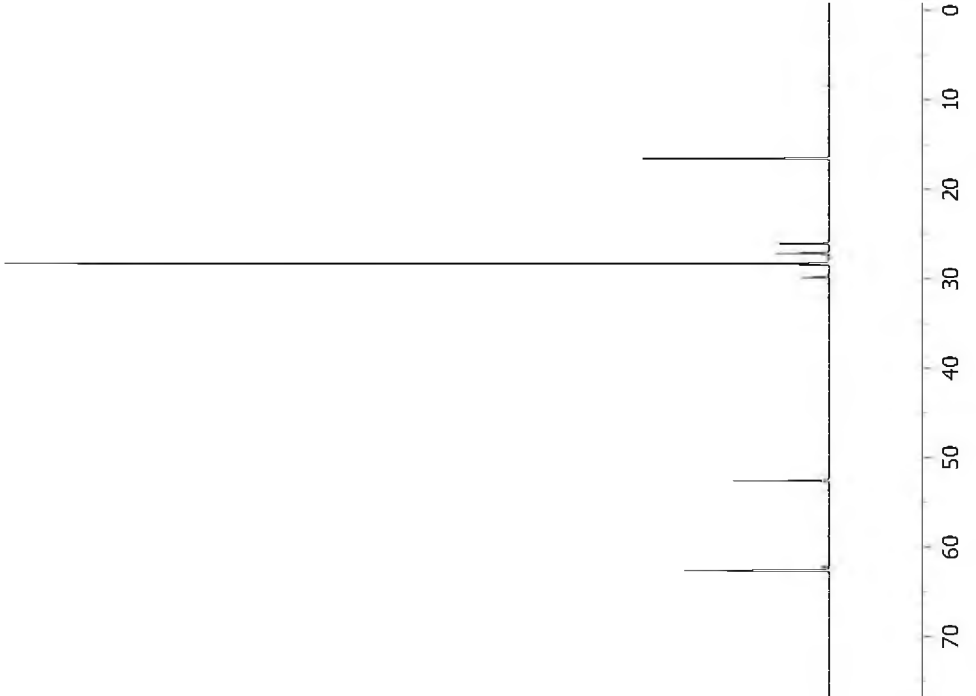

0.5
1.0
1.5
2.0
2.5
3.0
6.61
9.64
1.85

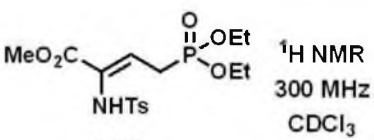


3.31

^{13}C NMR
125 MHz
$CDCl_3$

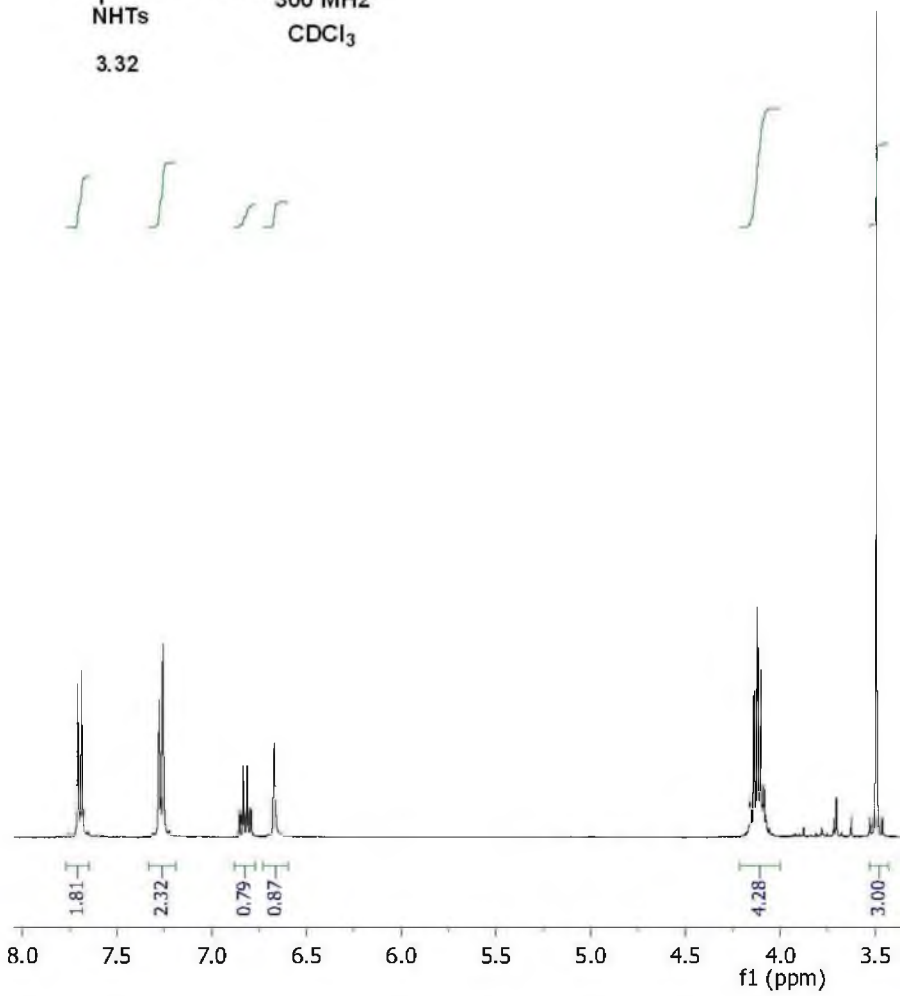


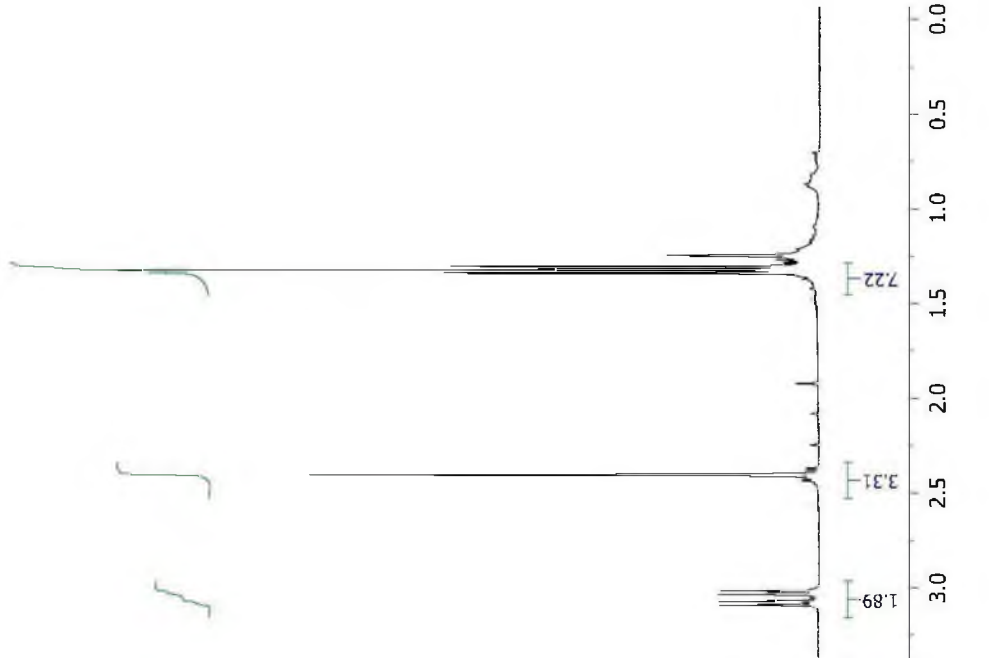

0
10
20
30
40
50
60
70

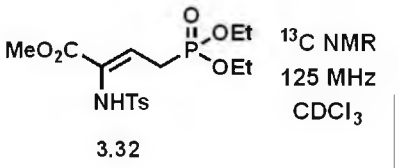


3.32

^{1}H NMR
300 MHz
$CDCl_3$

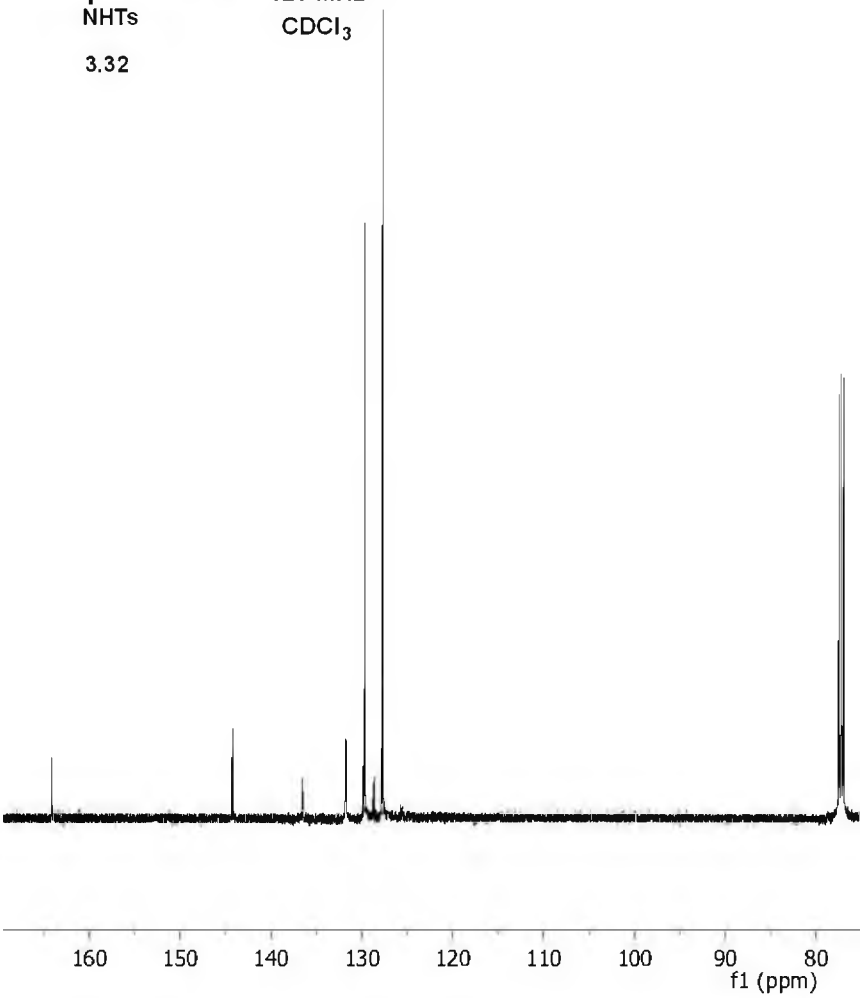


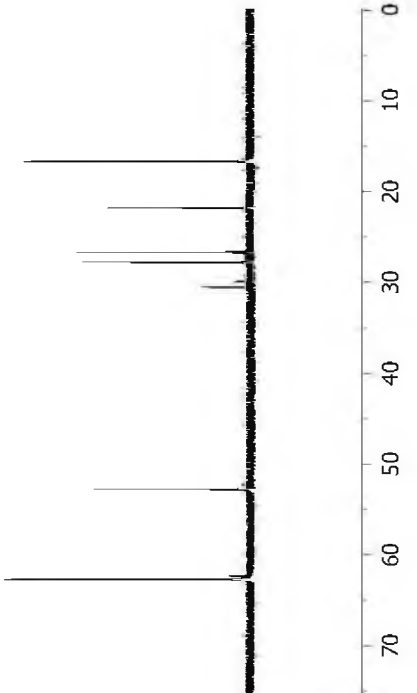

7.22
3.31
1.89
0.0
0.5
1.0
1.5
2.0
2.5
3.0

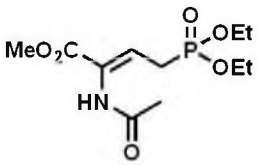


3.32

^{13}C NMR
125 MHz
$CDCl_3$

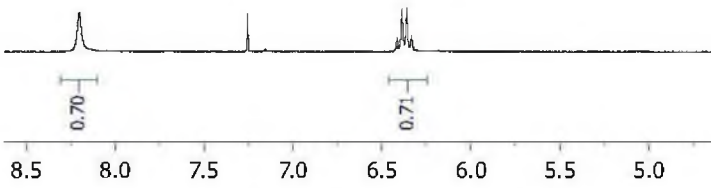


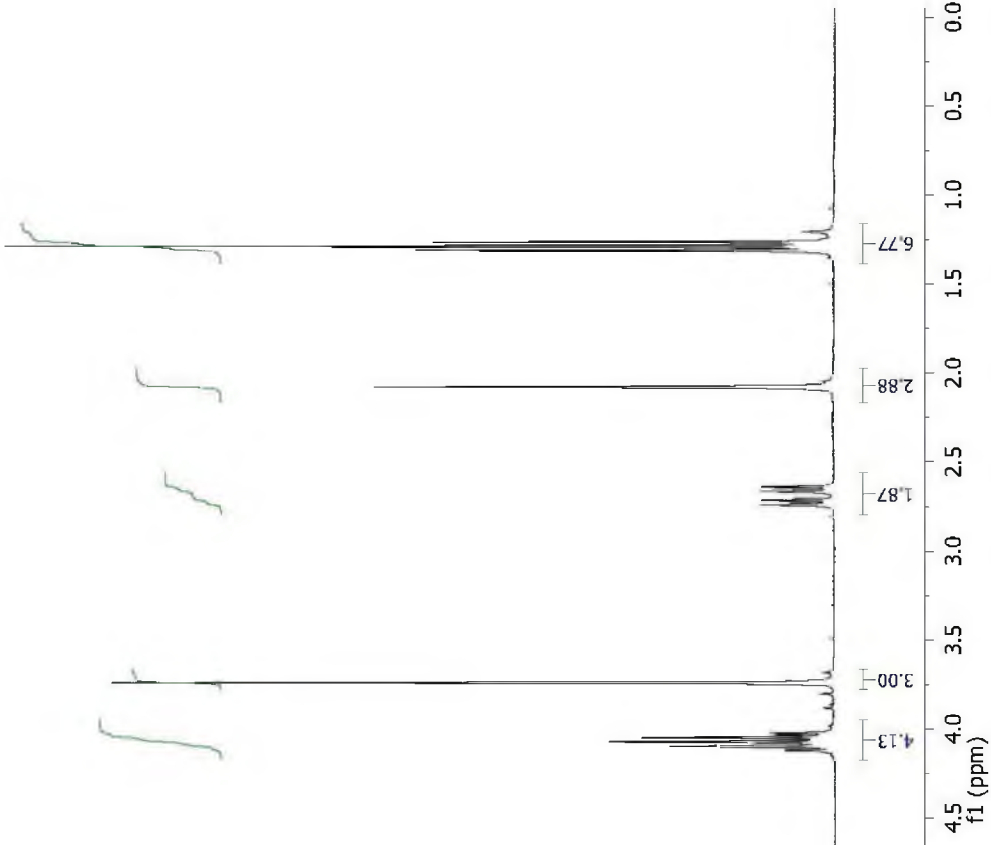

0
10
20
30
40
50
60
70

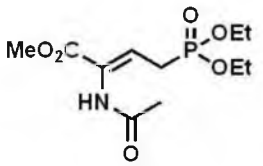


^{1}H NMR
300 MHz
$CDCl_3$

3.33

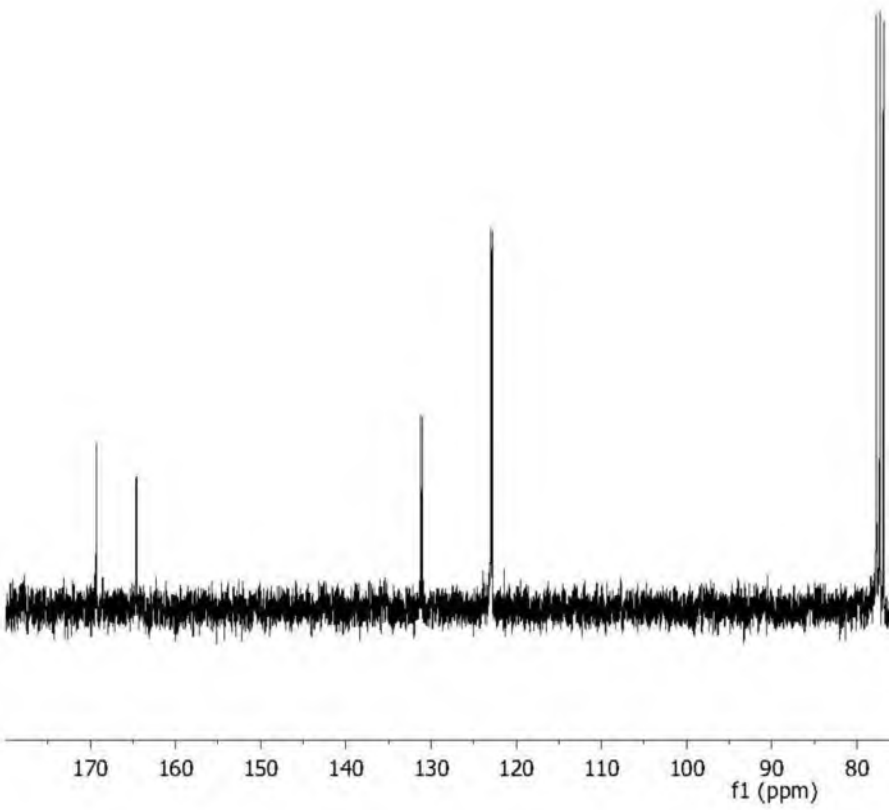


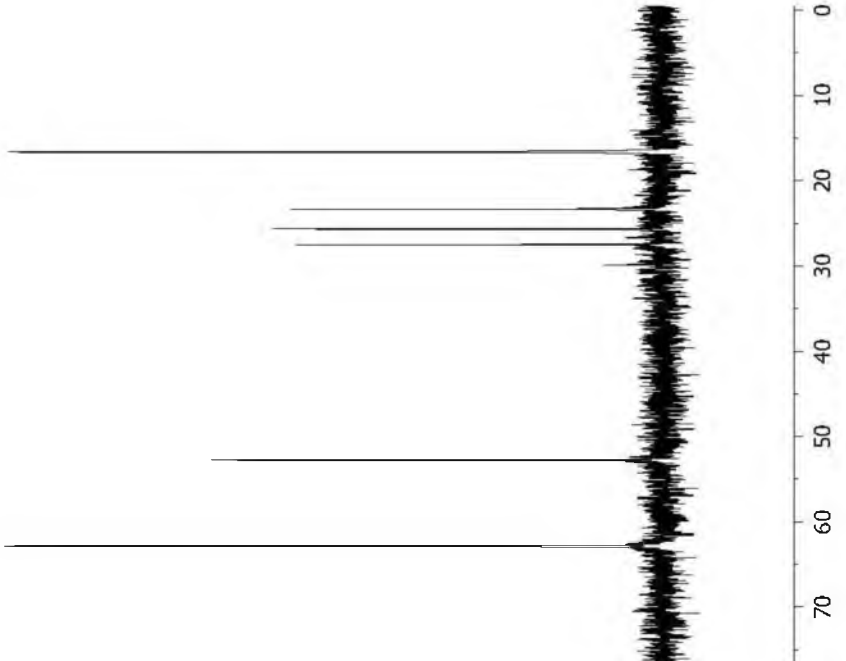

6.77
2.88
1.87
3.00
4.13
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

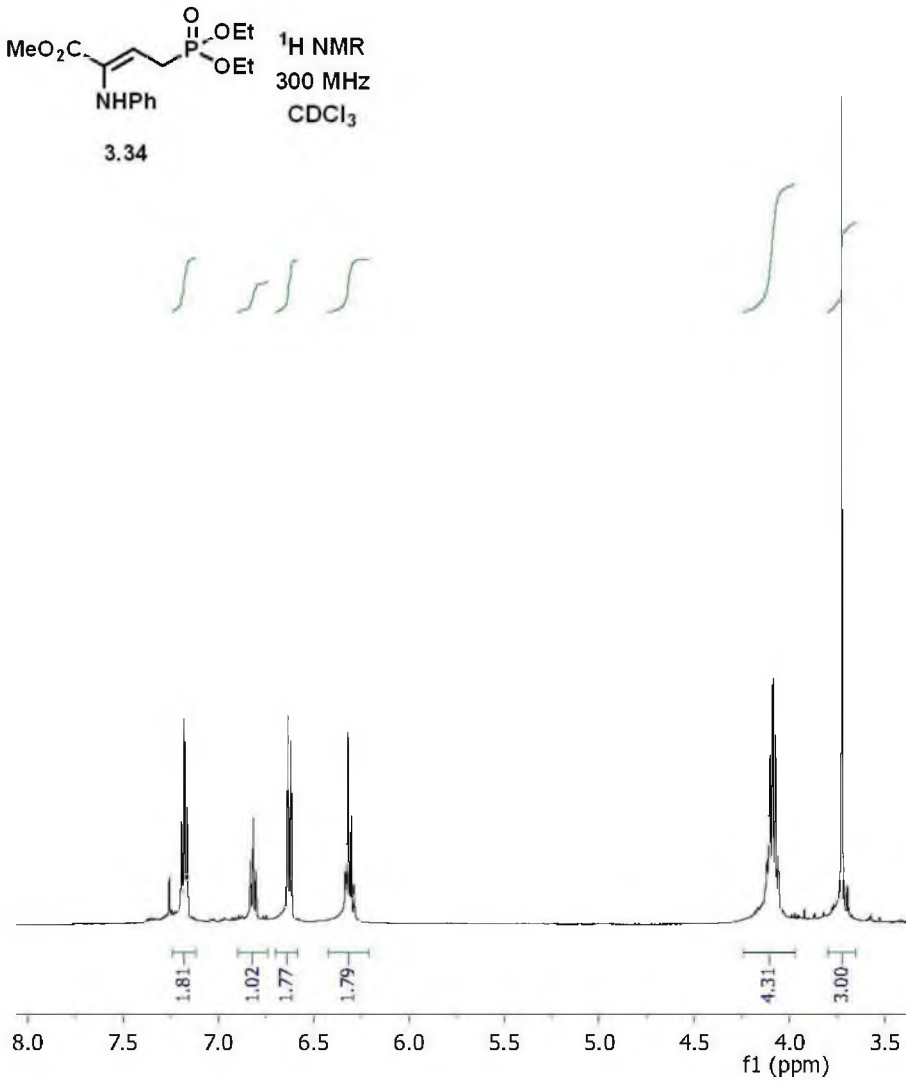


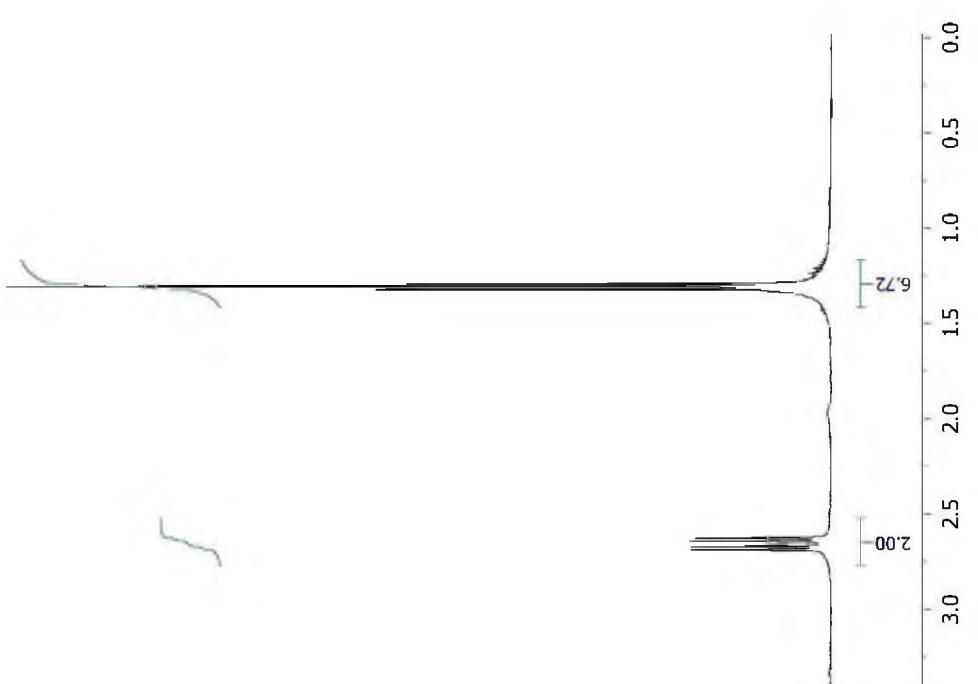
3.33

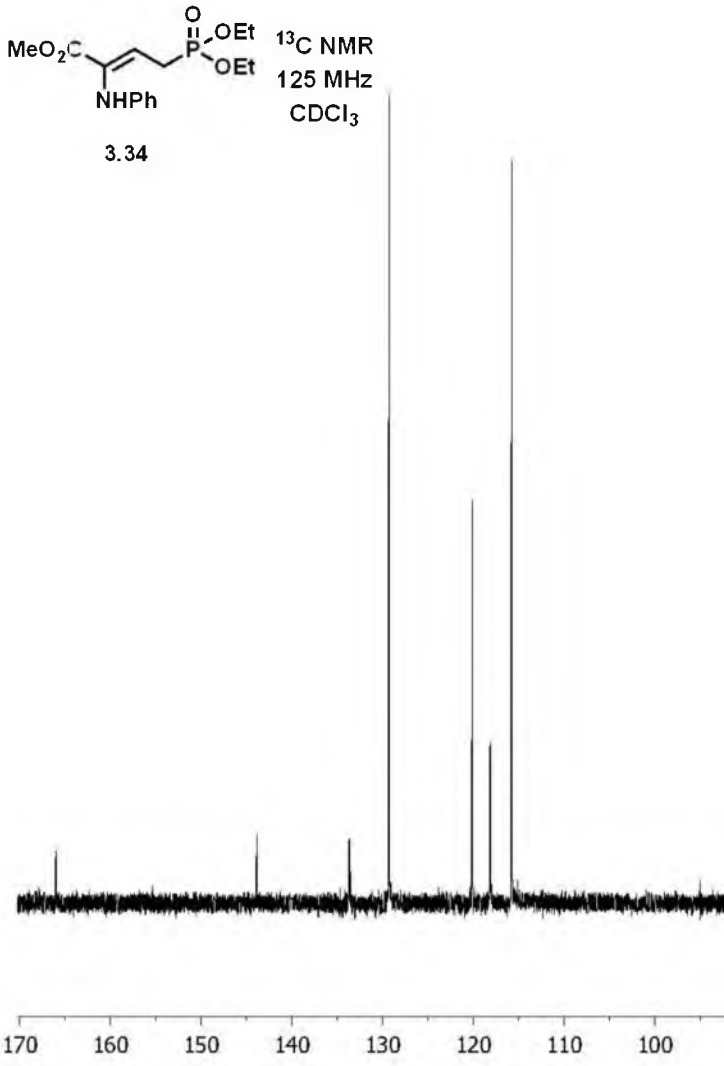
^{13}C NMR
75 MHz
$CDCl_3$

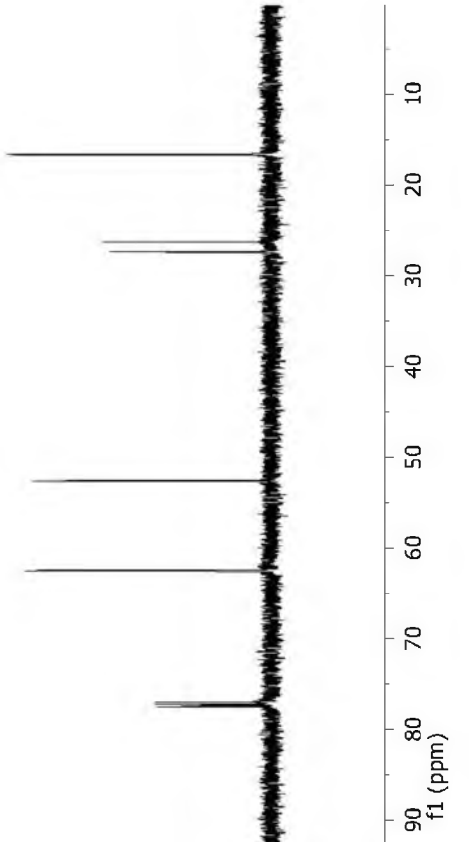


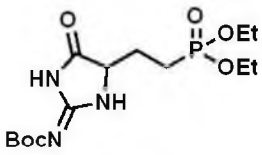

0
10
20
30
40
50
60
70


MeO2C
O
OEt
P
OEt
NHPh
3.34
1H NMR
300 MHz
CDCl3
1.81
1.02
1.77
1.79
4.31
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)


6.72
2.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0

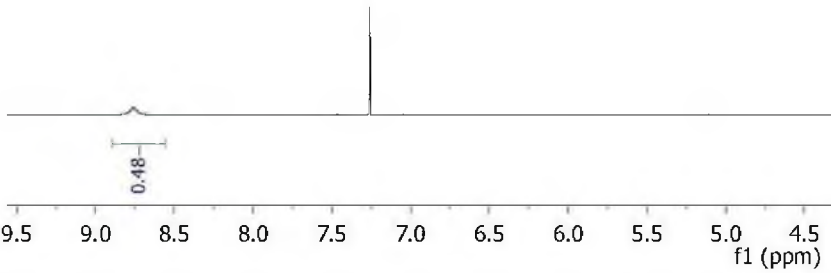

MeO2C
O
OEt
P
OEt
NHPh
3.34
13C NMR
125 MHz
CDCl3
170
160
150
140
130
120
110
100

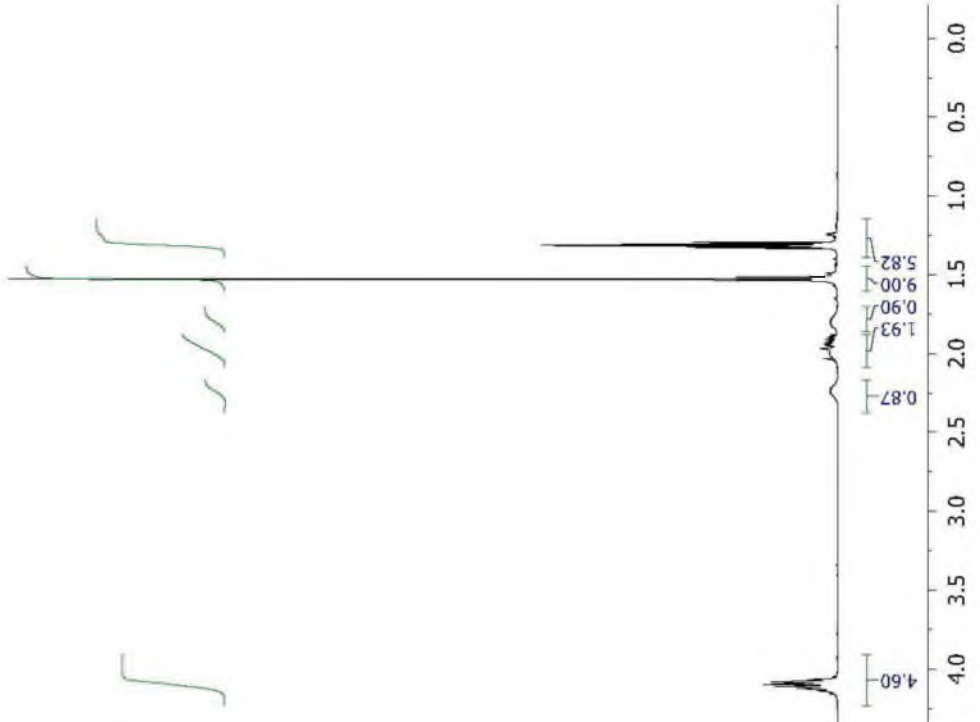

10
20
30
40
50
60
70
80
90
f1 (ppm)

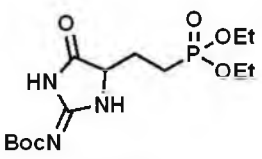


3.36

^{1}H NMR
500 MHz
$CDCl_3$

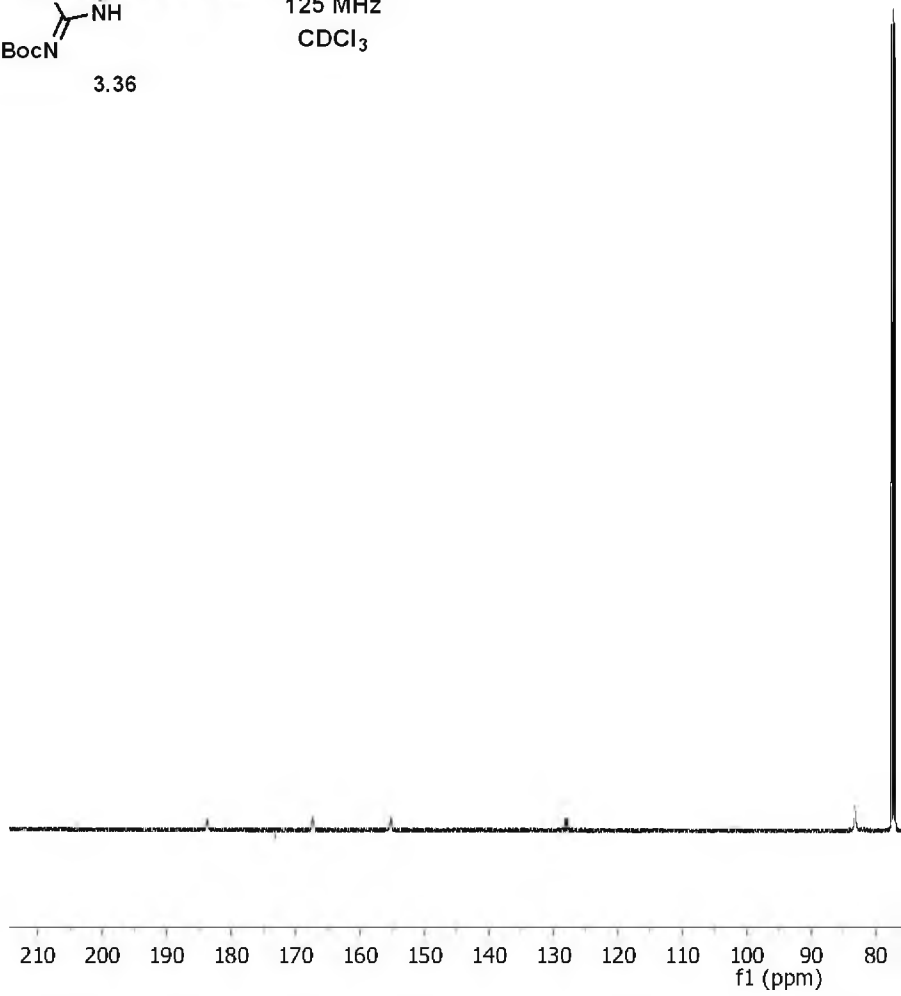


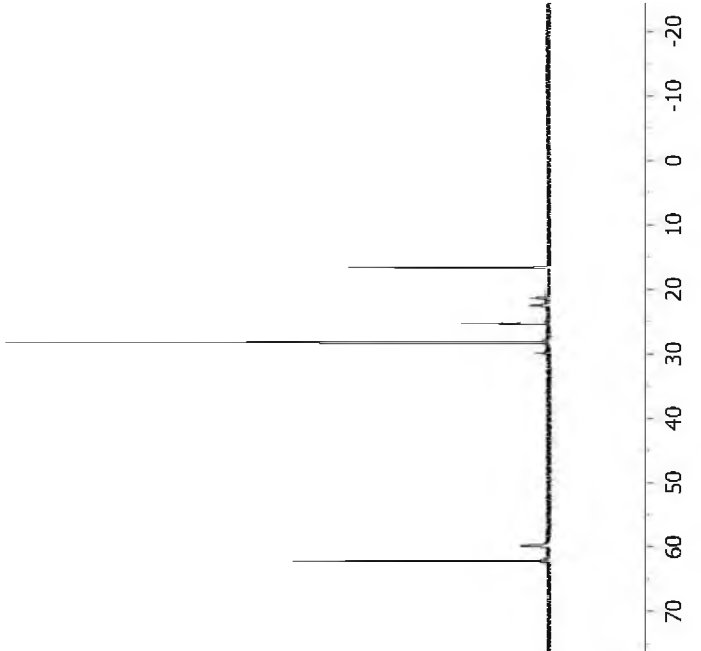

4.60
0.87
1.93
0.90
9.00
5.82
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

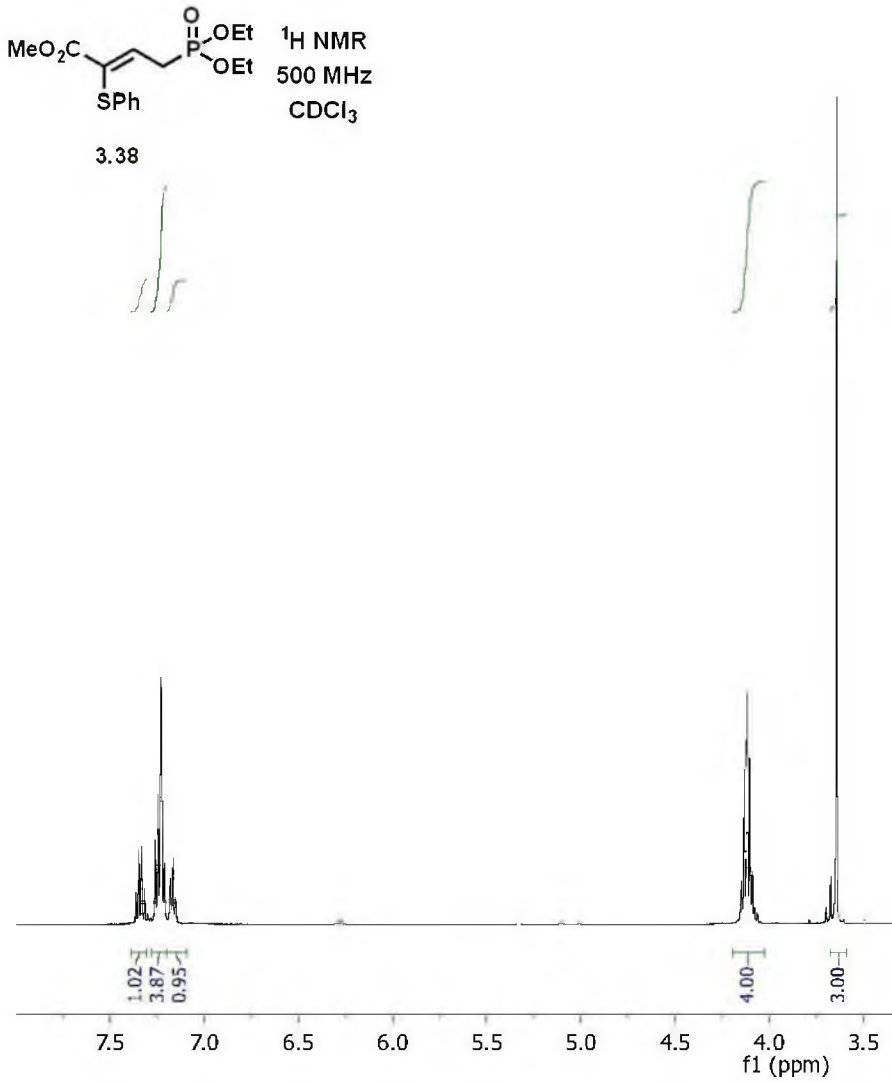


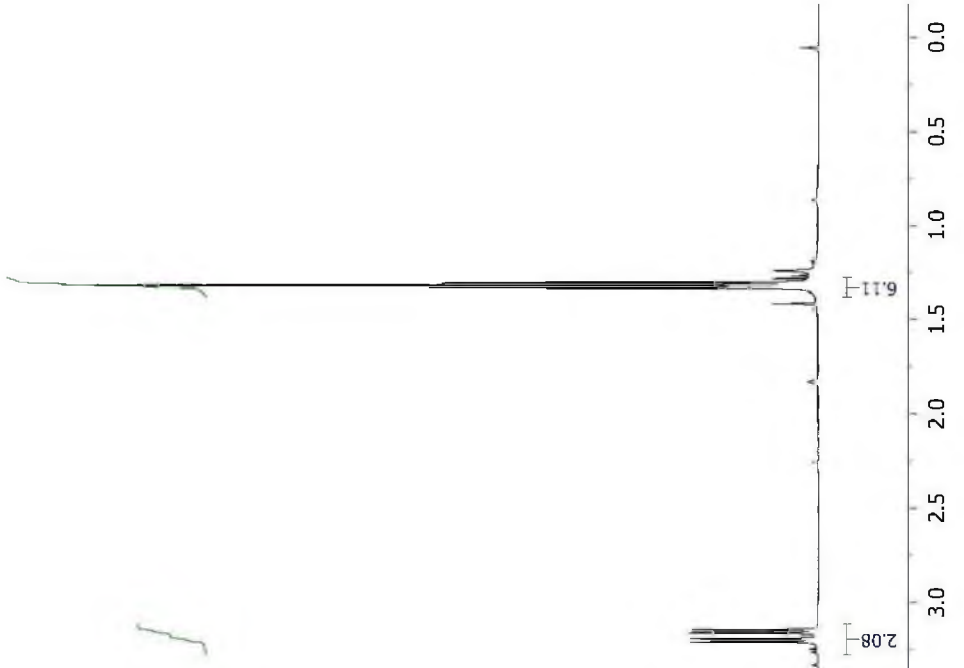
3.36

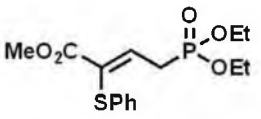
^{13}C NMR
125 MHz
$CDCl_3$




70
60
50
40
30
20
10
0
-10
-20

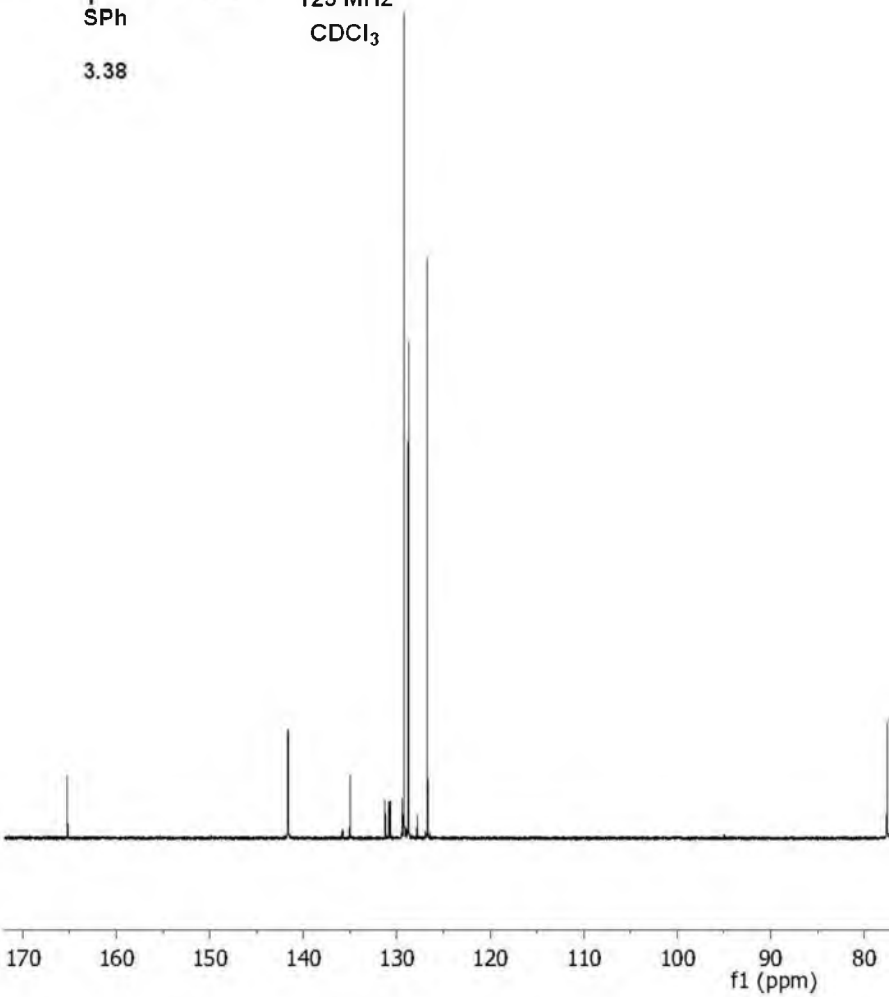

MeO2C
O
P
OEt
OEt
SPh
1H NMR
500 MHz
CDCl3
3.38
1.02
3.87
0.95
4.00
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

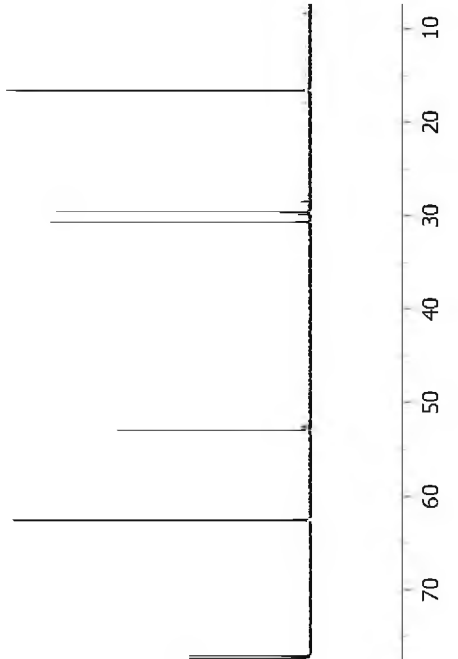

6.11
2.08
0.0
0.5
1.0
1.5
2.0
2.5
3.0

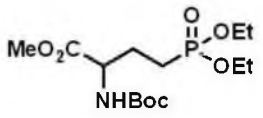


3.38

^{13}C NMR
125 MHz
$CDCl_3$

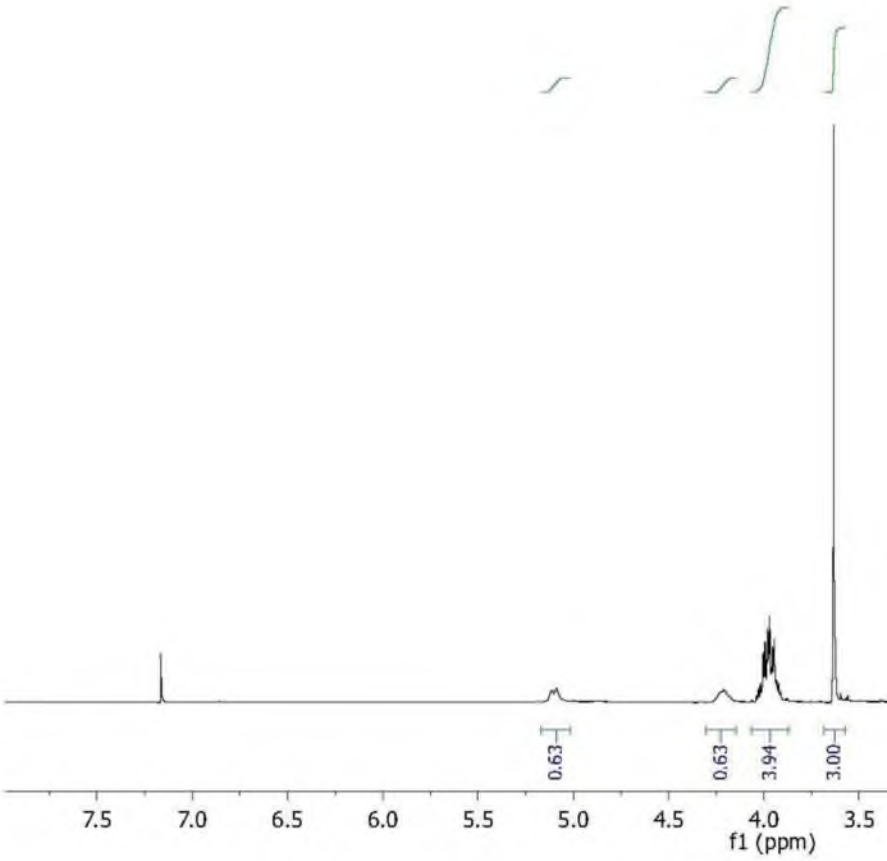


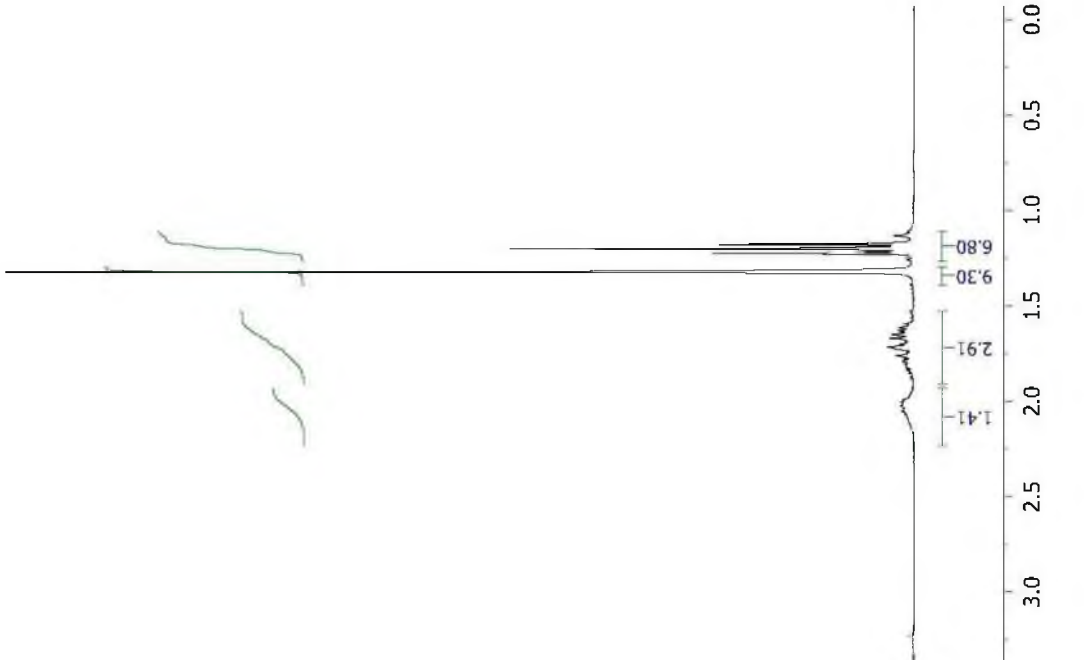

10
20
30
40
50
60
70

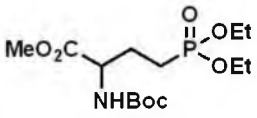


3.42

^{1}H NMR
300 MHz
$CDCl_3$

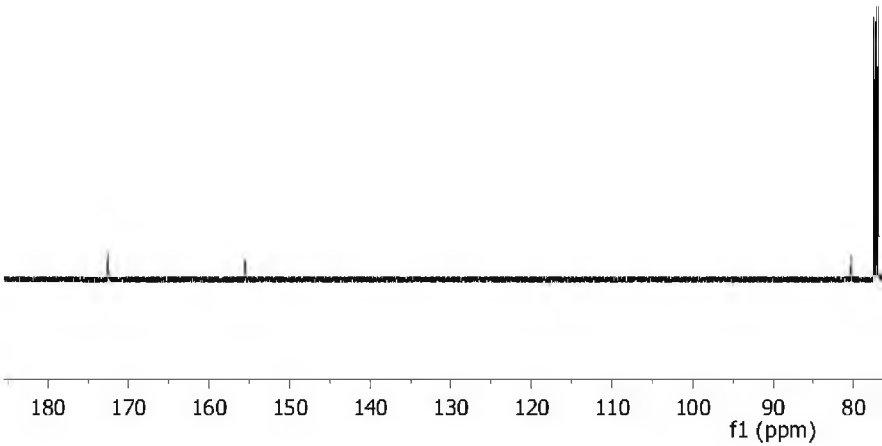


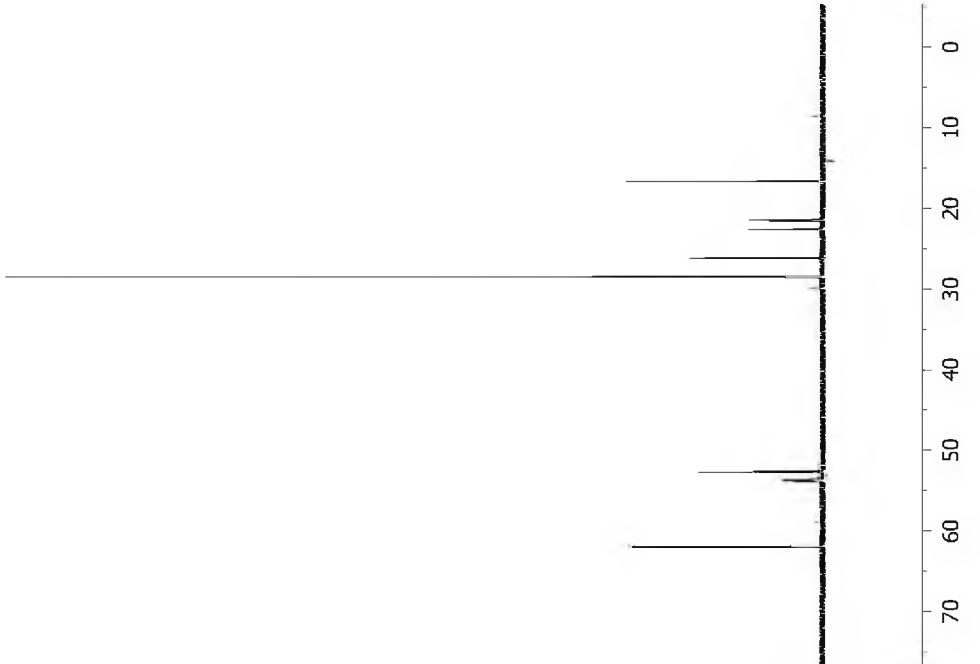

6.80
9.30
2.91
1.41
0.0
0.5
1.0
1.5
2.0
2.5
3.0

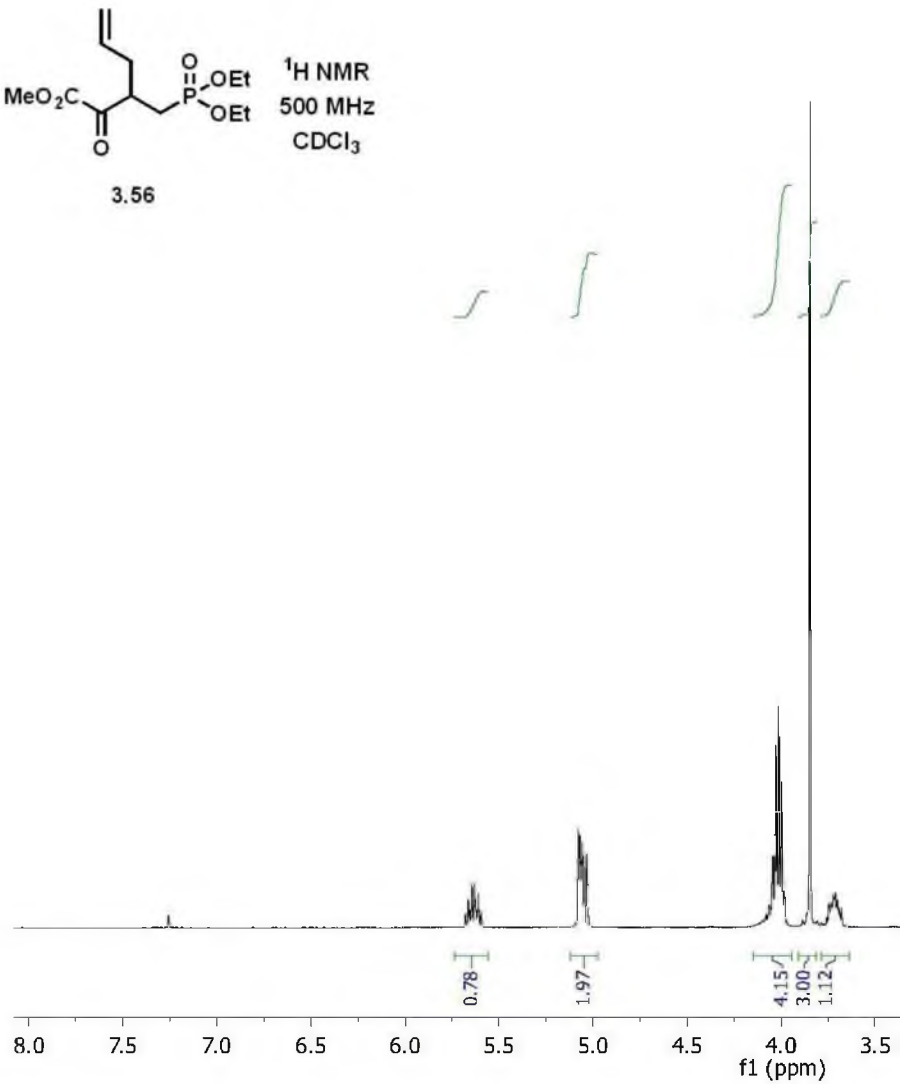


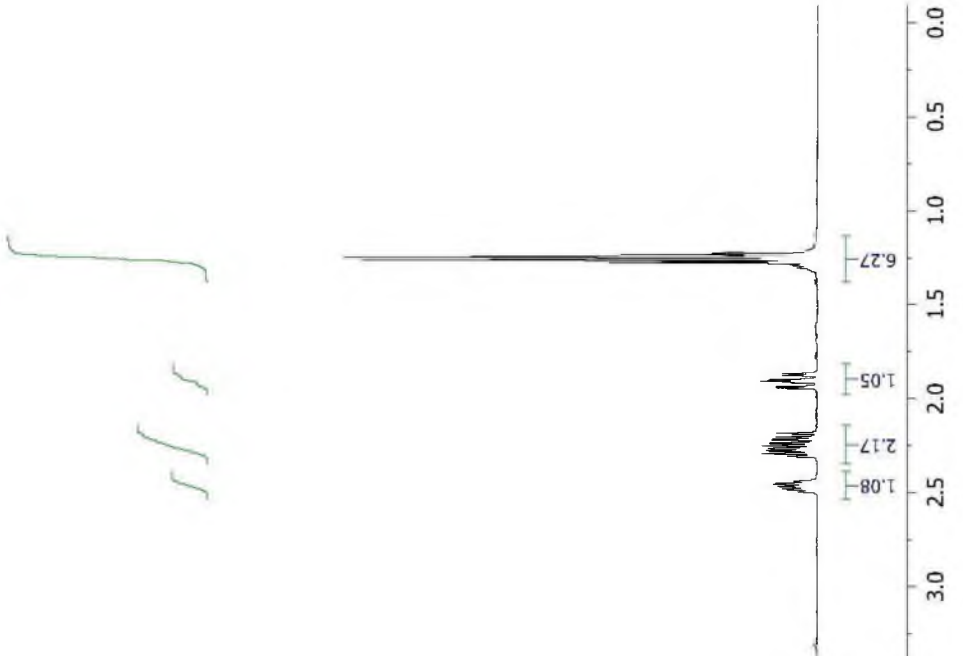
3.42

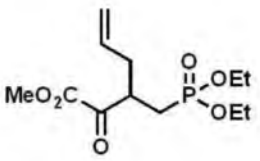
^{13}C NMR
125 MHz
$CDCl_3$




0
10
20
30
40
50
60
70

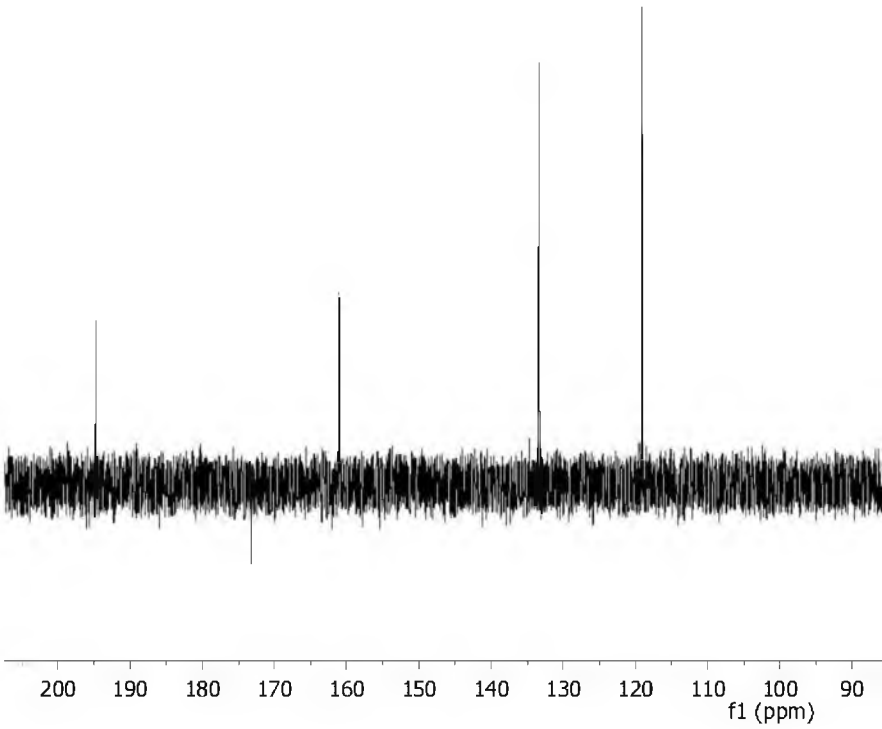

MeO2C
O
OEt
P
OEt
O
3.56
1H NMR
500 MHz
CDCl3
0.78
1.97
4.15
3.00
1.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

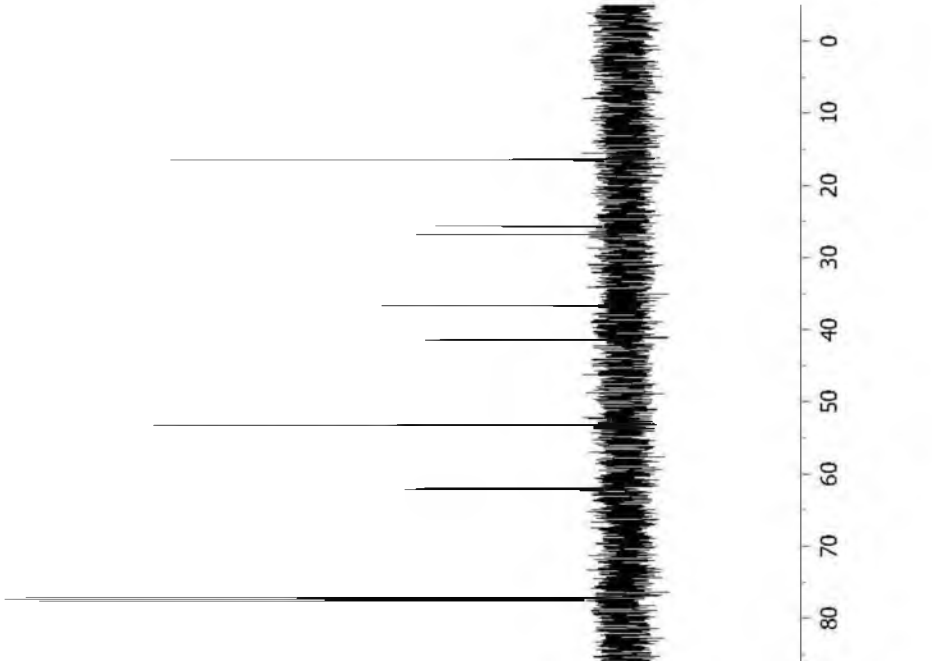

6.27
1.05
2.17
1.08
0.0
0.5
1.0
1.5
2.0
2.5
3.0

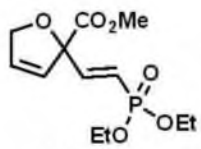


^{13}C NMR
125 MHz
$CDCl_3$

3.56

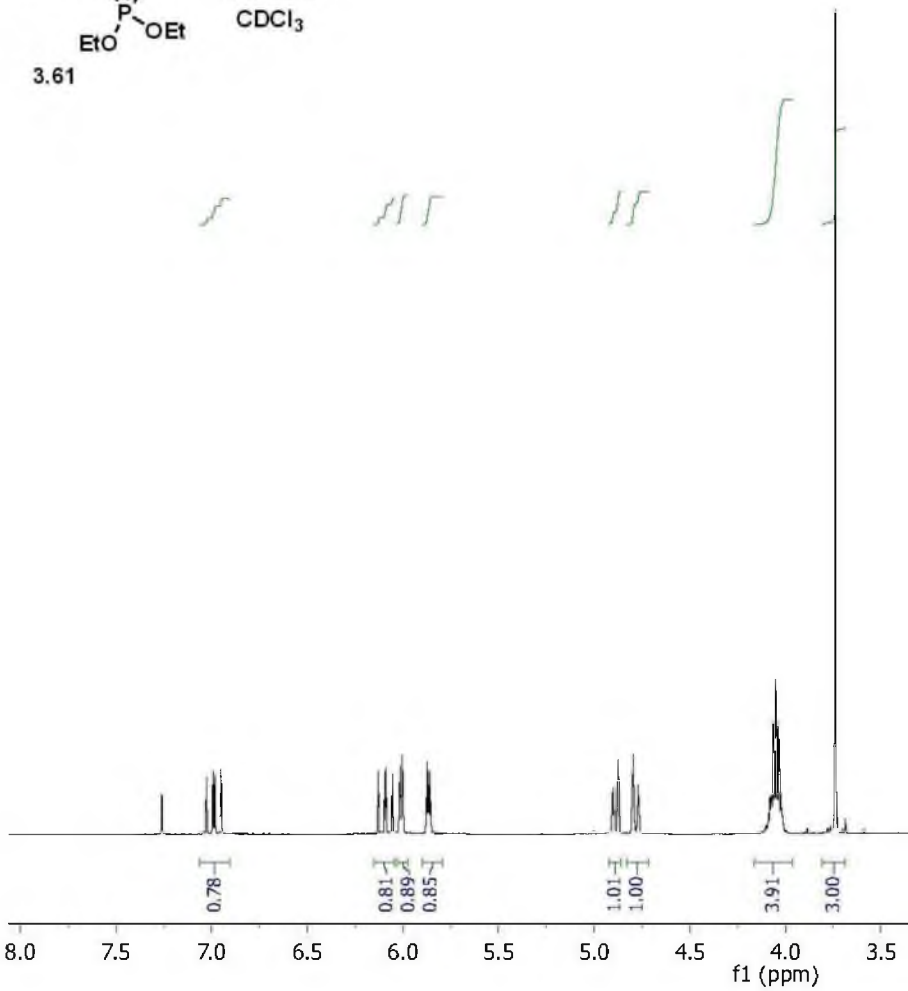


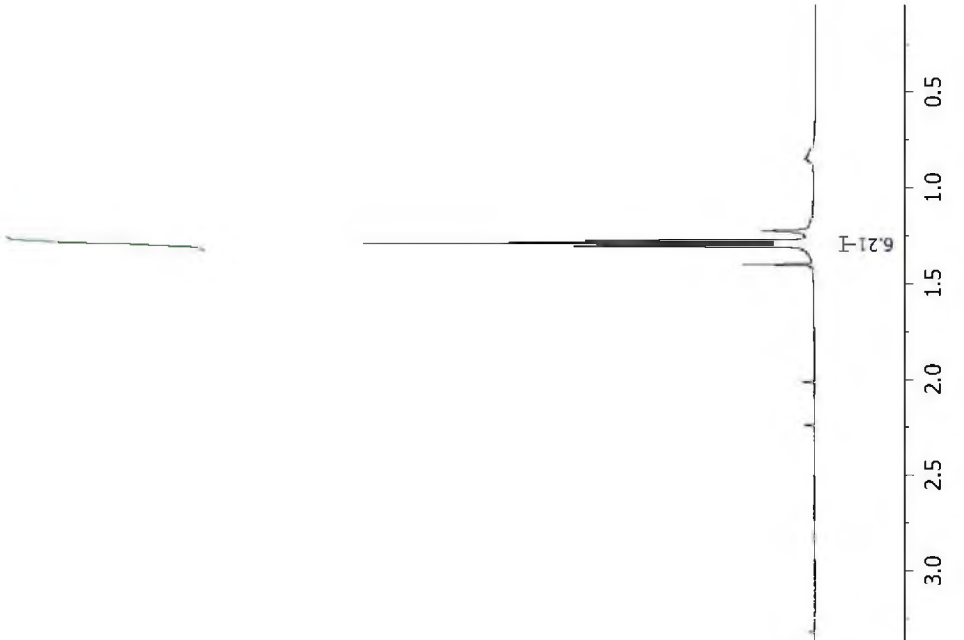

0
10
20
30
40
50
60
70
80

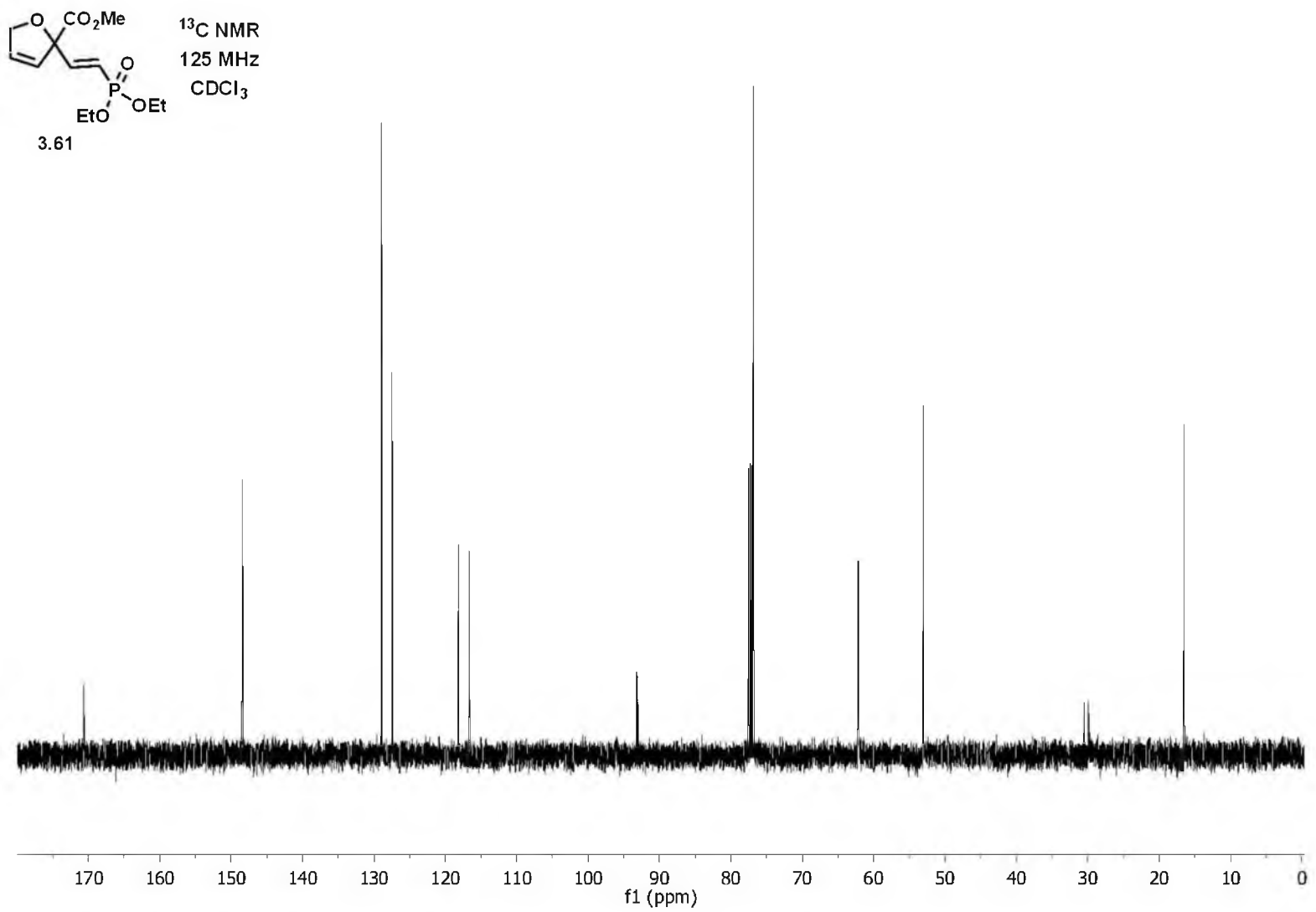


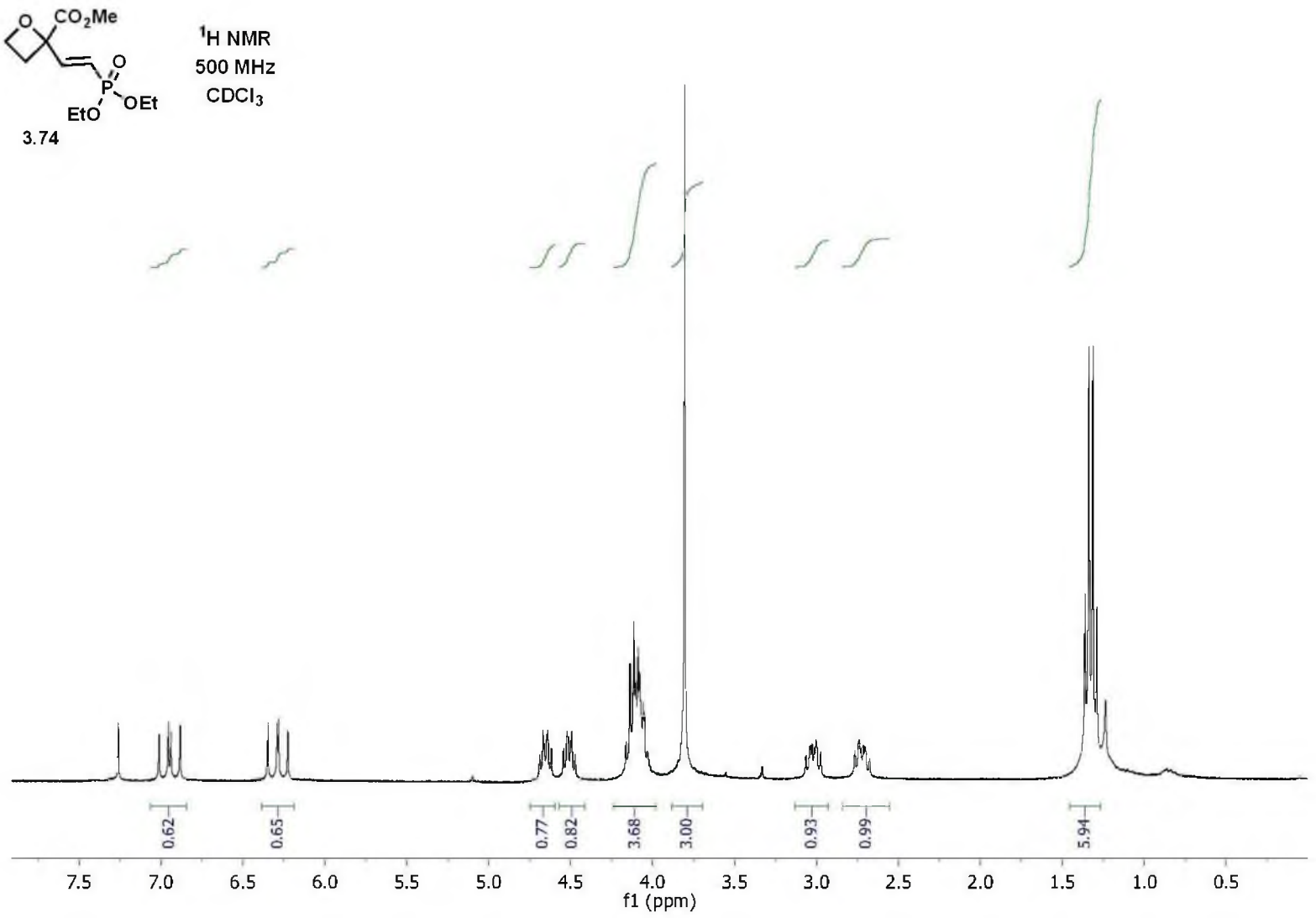
3.61

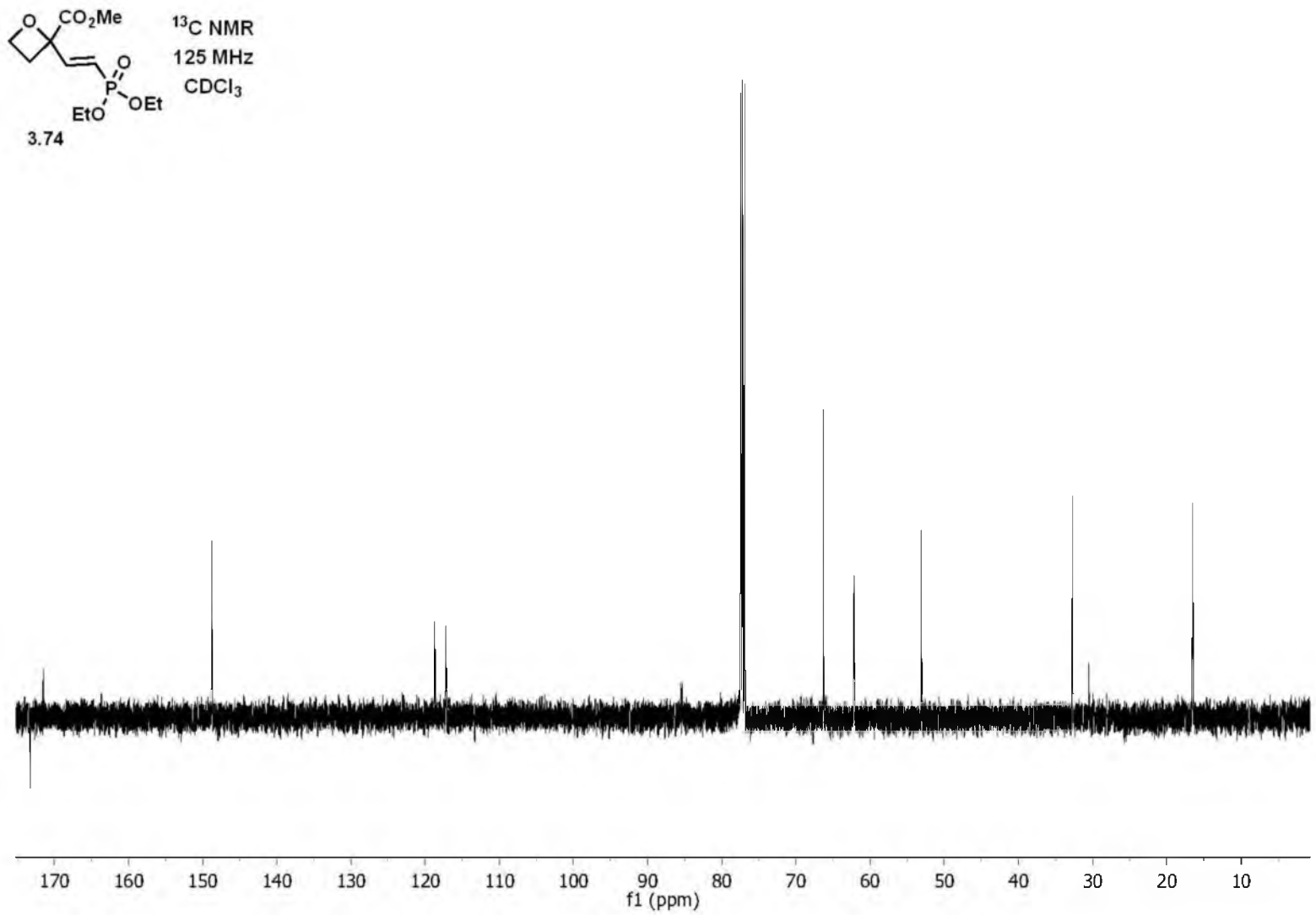
^{1}H NMR
500 MHz
$CDCl_3$

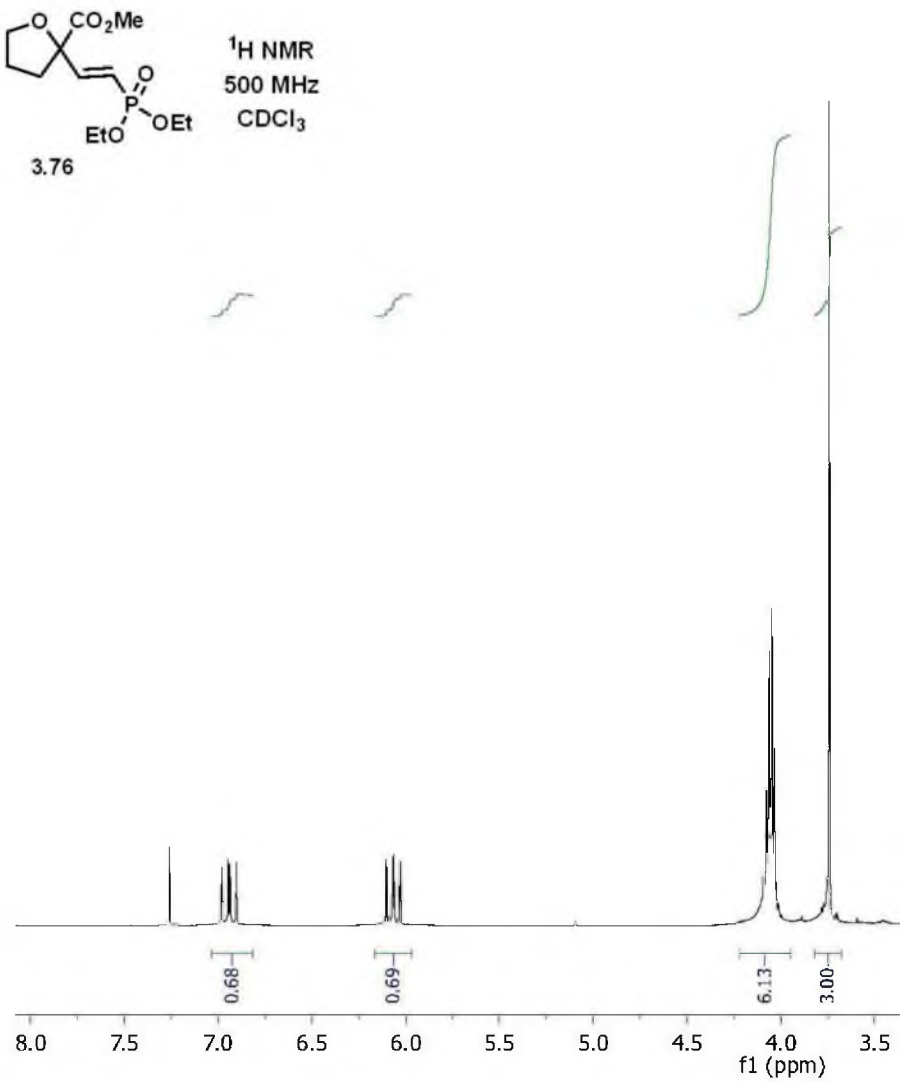


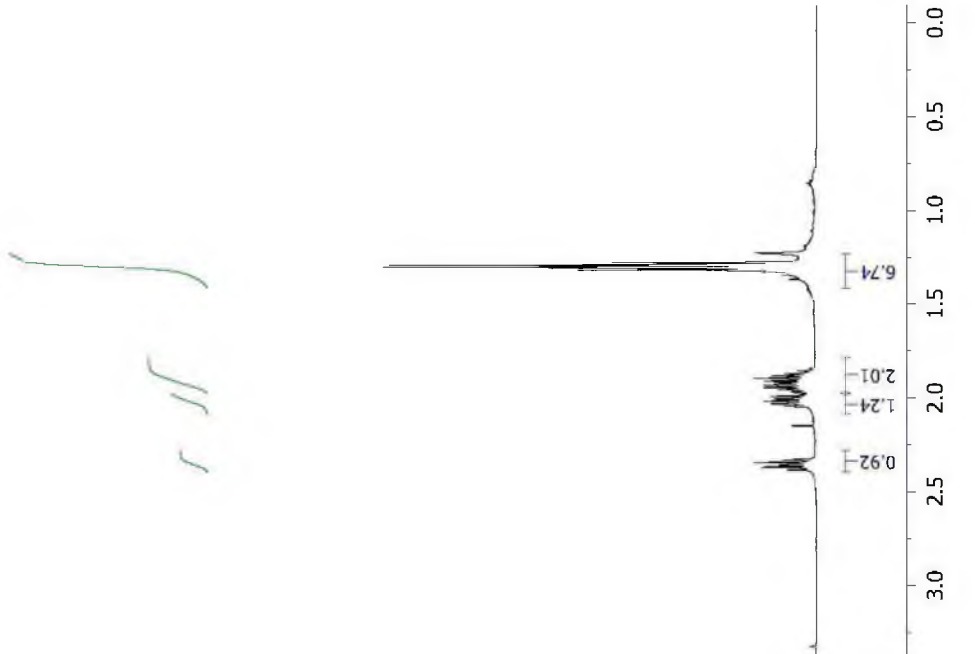

6.21-I
0.5
1.0
1.5
2.0
2.5
3.0

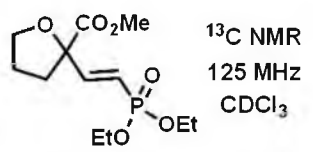

CO2Me
O
O
P
OEt
EtO
3.61
13C NMR
125 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CO2Me
O
O
P
OEt
EtO
3.74
1H NMR
500 MHz
CDCl3
0.62
0.65
0.77
0.82
3.68
3.00
0.93
0.99
5.94
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CO2Me
O
O
P
EtO
OEt
3.74
13C NMR
125 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

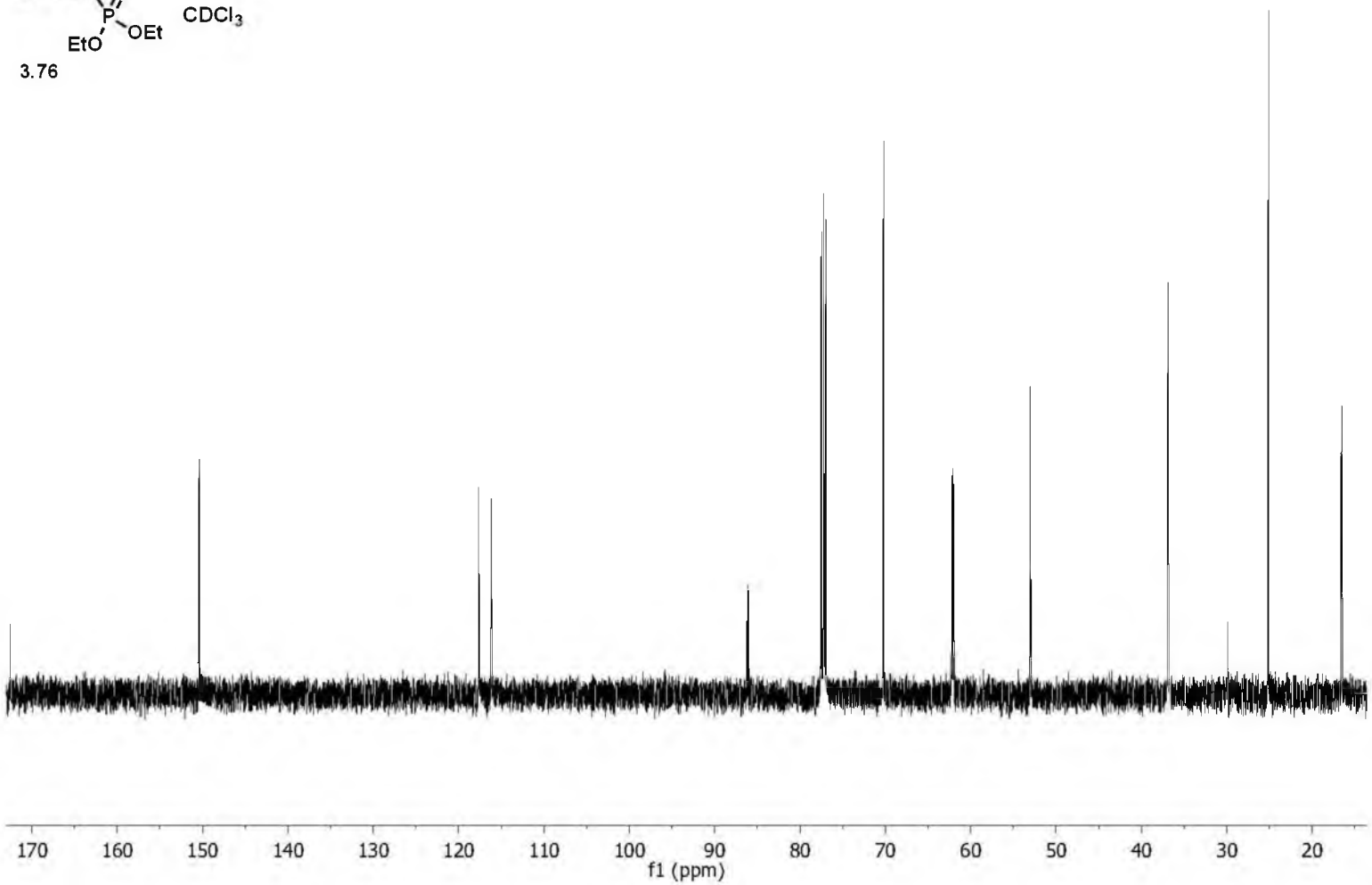

CO2Me
O
O
P
EtO
OEt
3.76
1H NMR
500 MHz
CDCl3
0.68
0.69
6.13
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)

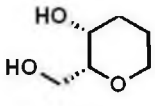

6.74
2.01
1.24
0.92
0.0
0.5
1.0
1.5
2.0
2.5
3.0



3.76

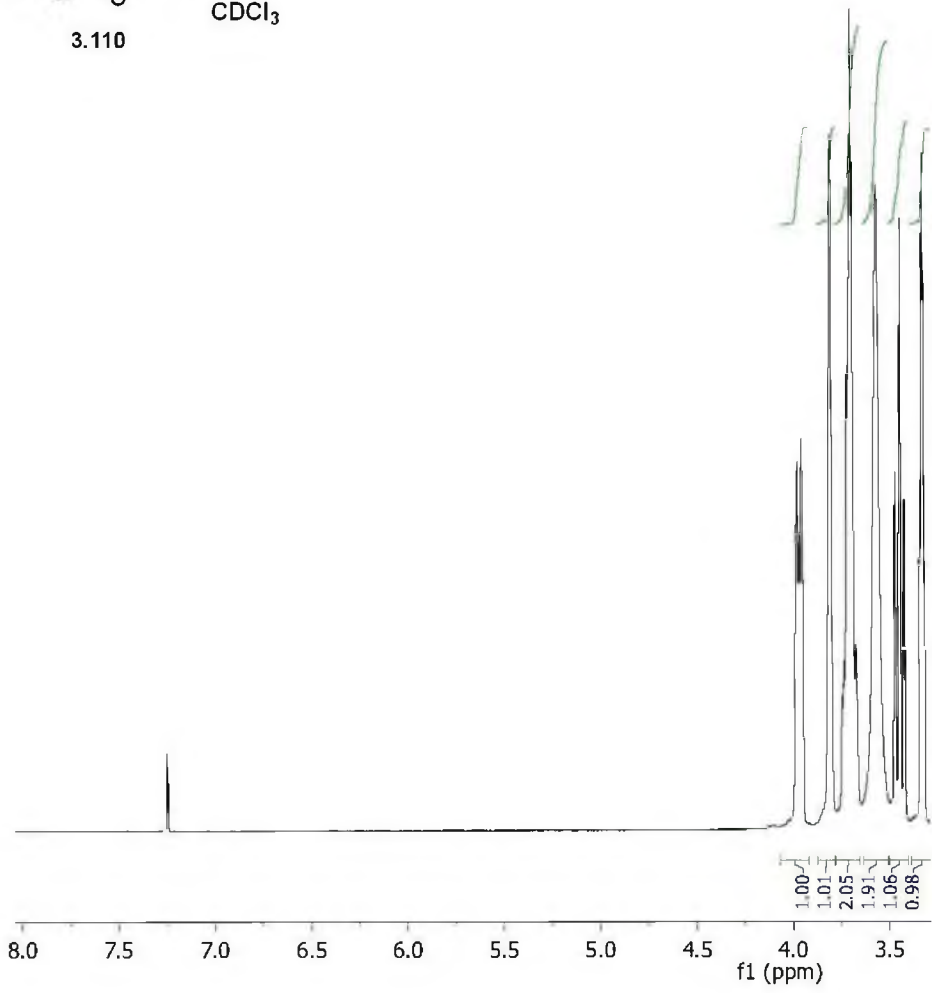
^{13}C NMR
125 MHz
$CDCl_3$

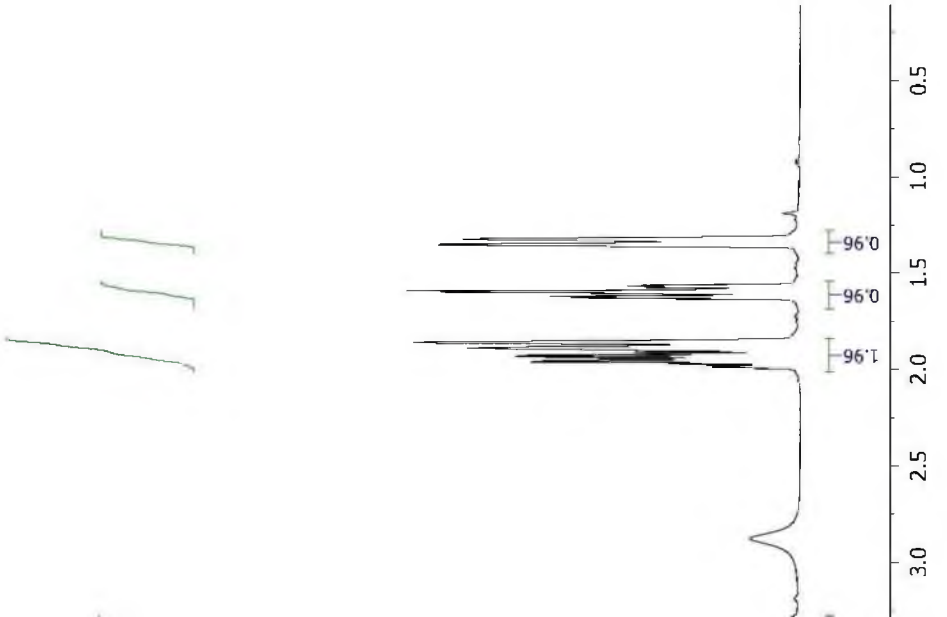


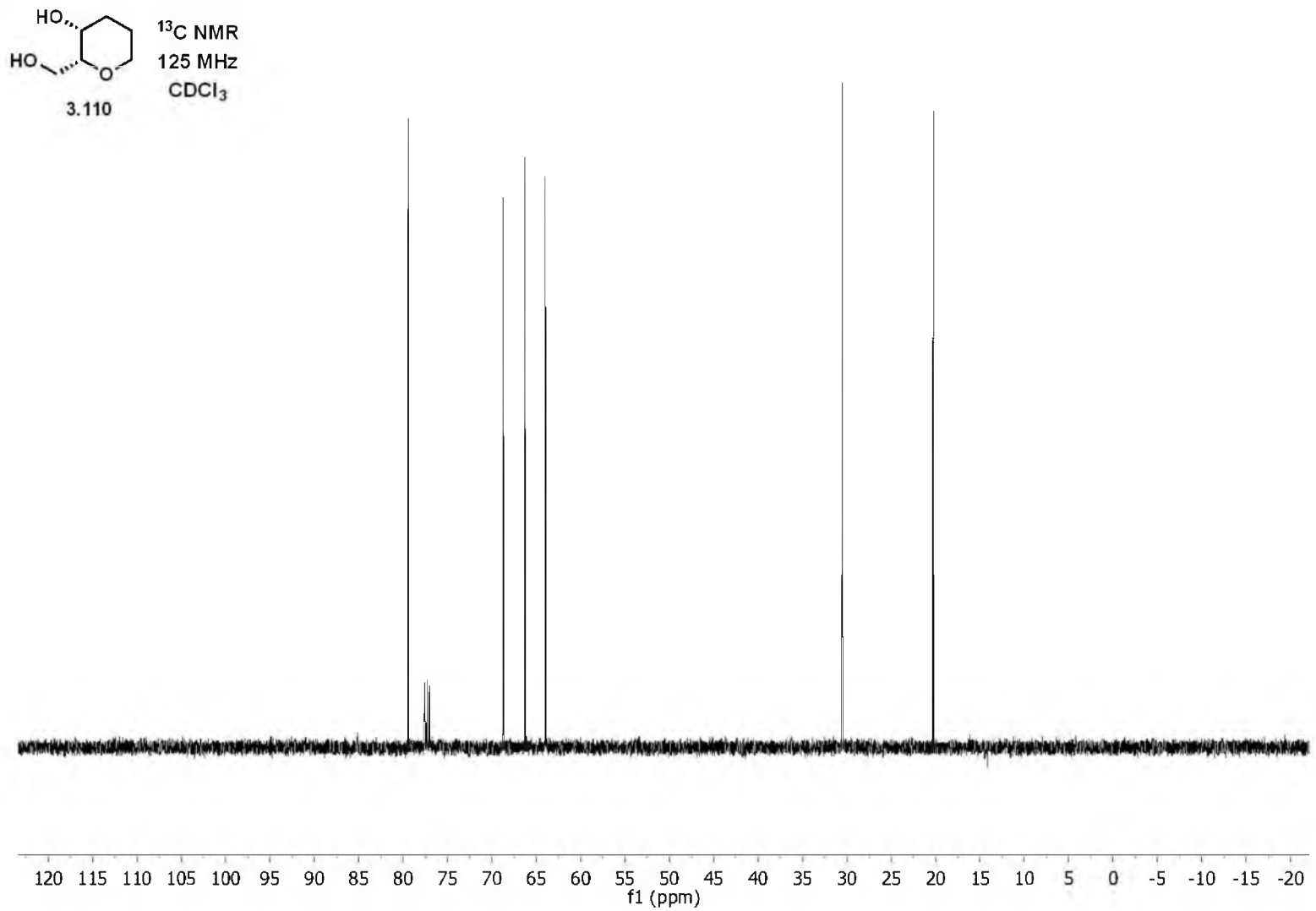


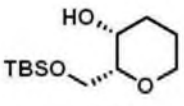
3.110

^{1}H NMR
500 MHz
$CDCl_3$



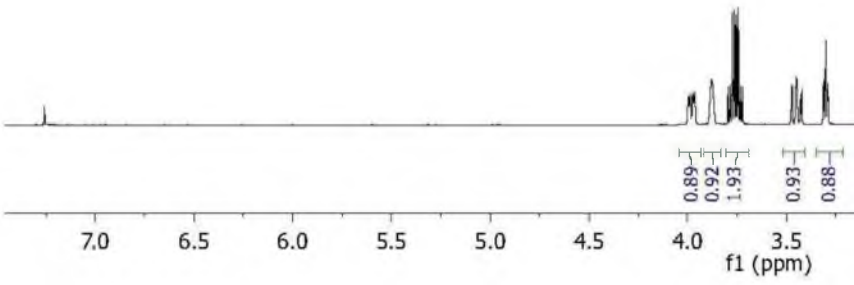

0.96
0.96
1.96
0.5
1.0
1.5
2.0
2.5
3.0


HO
HO
O
3.110
13C NMR
125 MHz
CDCl3
120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20
f1 (ppm)

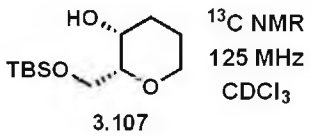


3.107

^{1}H NMR
500 MHz
$CDCl_3$

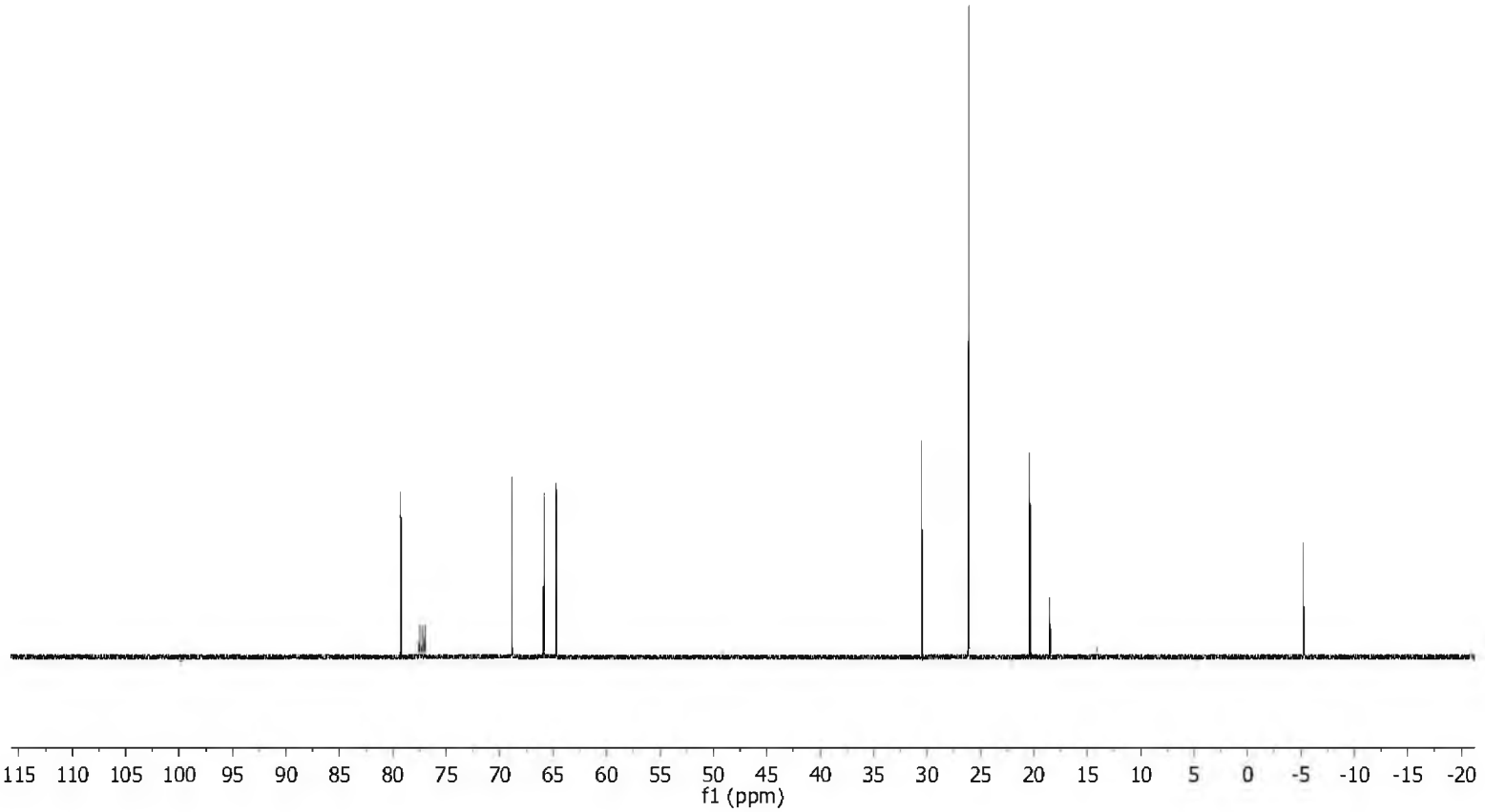


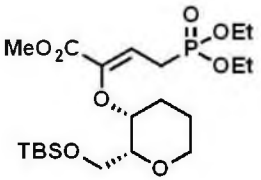

5.49
9.00
0.87
0.89
2.00
0.80
0.0
0.5
1.0
1.5
2.0
2.5
3.0



3.107

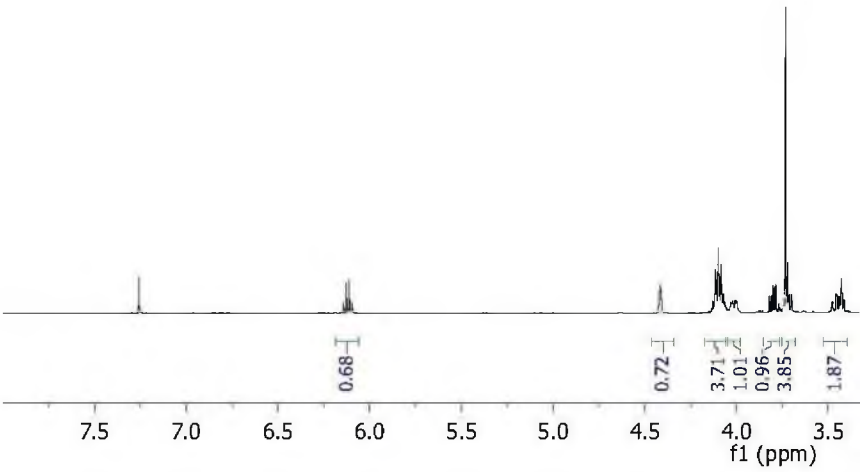
^{13}C NMR
125 MHz
$CDCl_3$

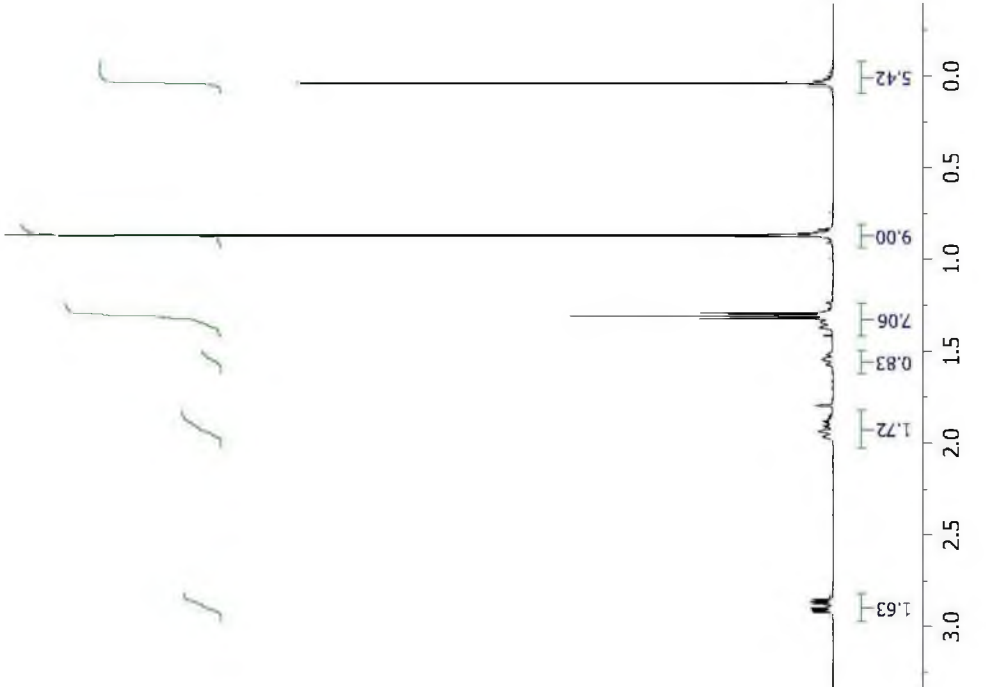


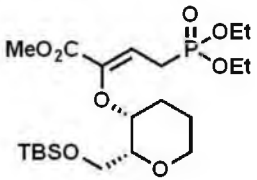


3.111

^{1}H NMR
500 MHz
$CDCl_3$

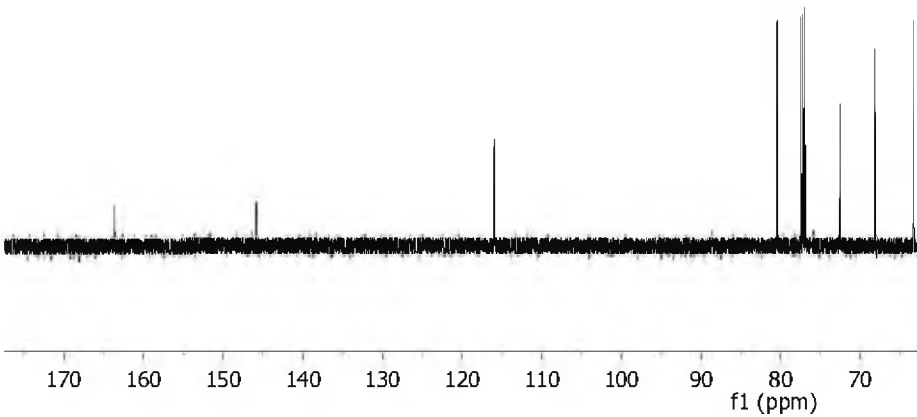



5.42
9.00
7.06
0.83
1.72
1.63
0.0
0.5
1.0
1.5
2.0
2.5
3.0

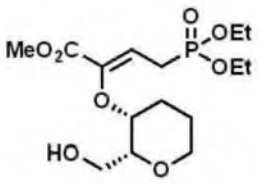


3.111

^{13}C NMR
125 MHz
$CDCl_3$

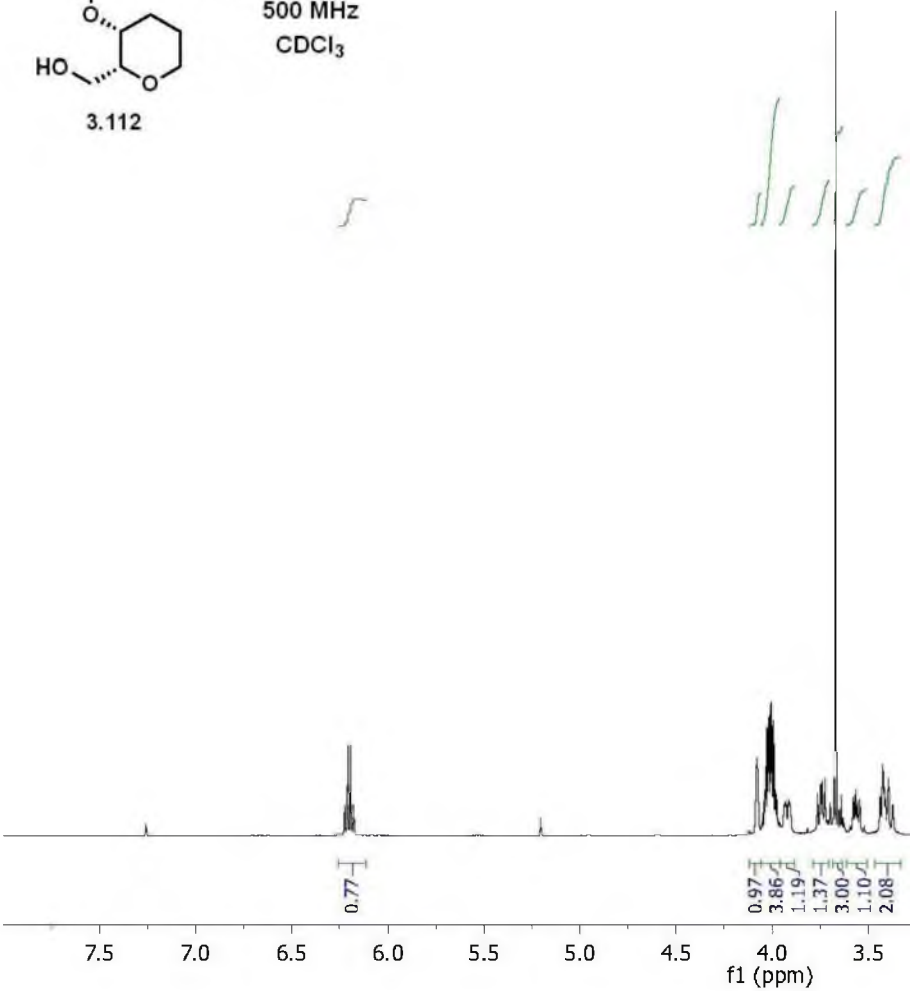


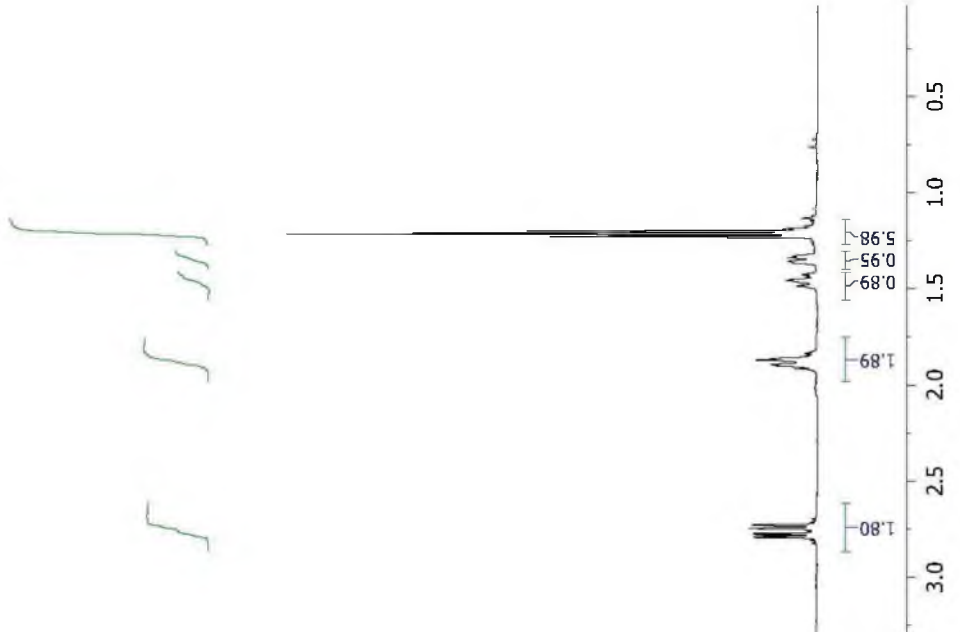

-10
0
10
20
30
40
50
60

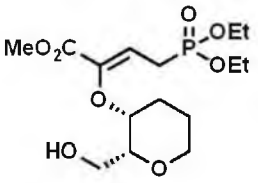


3.112

^{1}H NMR
500 MHz
$CDCl_3$

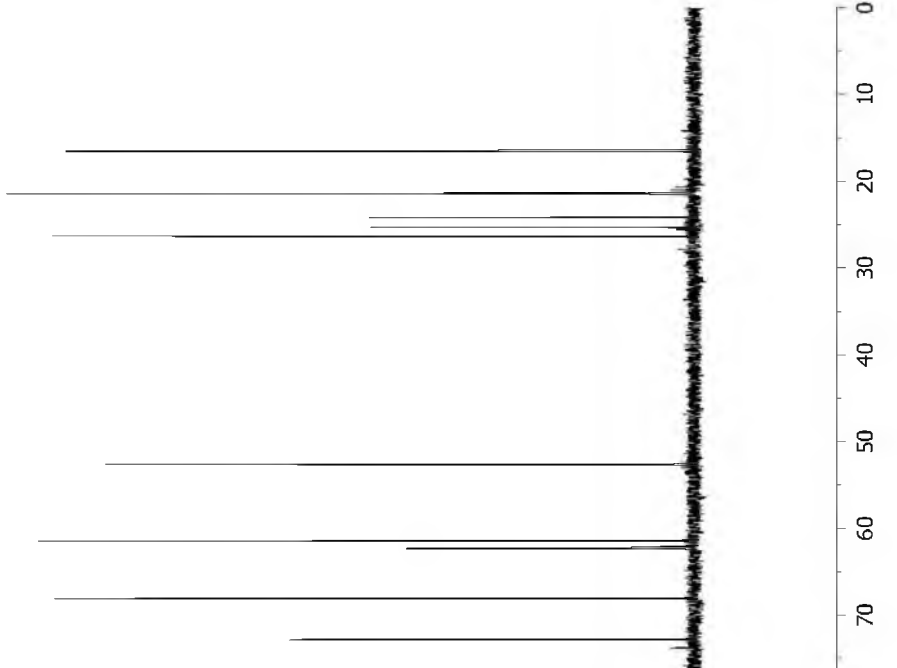


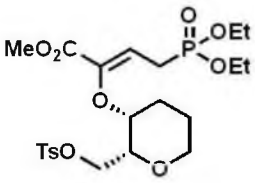

5.98
0.95
0.89
1.89
1.80
0.5
1.0
1.5
2.0
2.5
3.0



3.112

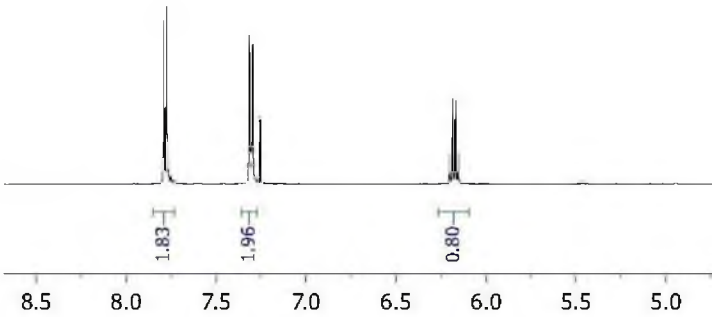
^{13}C NMR
125 MHz
$CDCl_3$

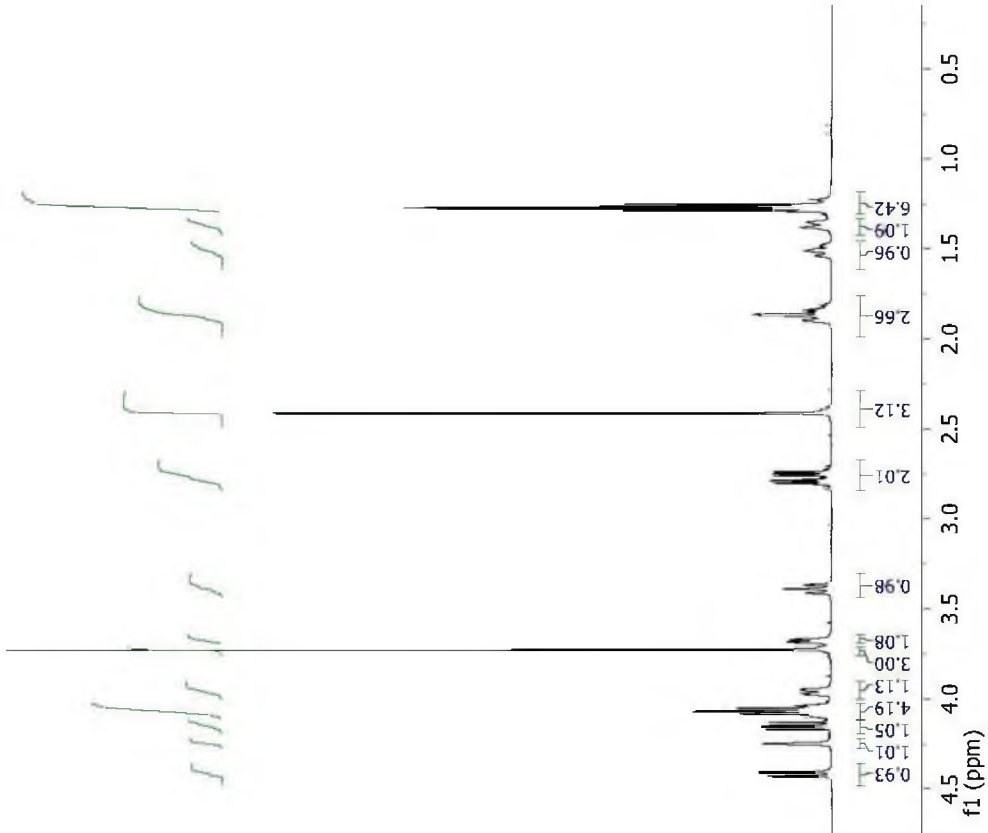

0
10
20
30
40
50
60
70

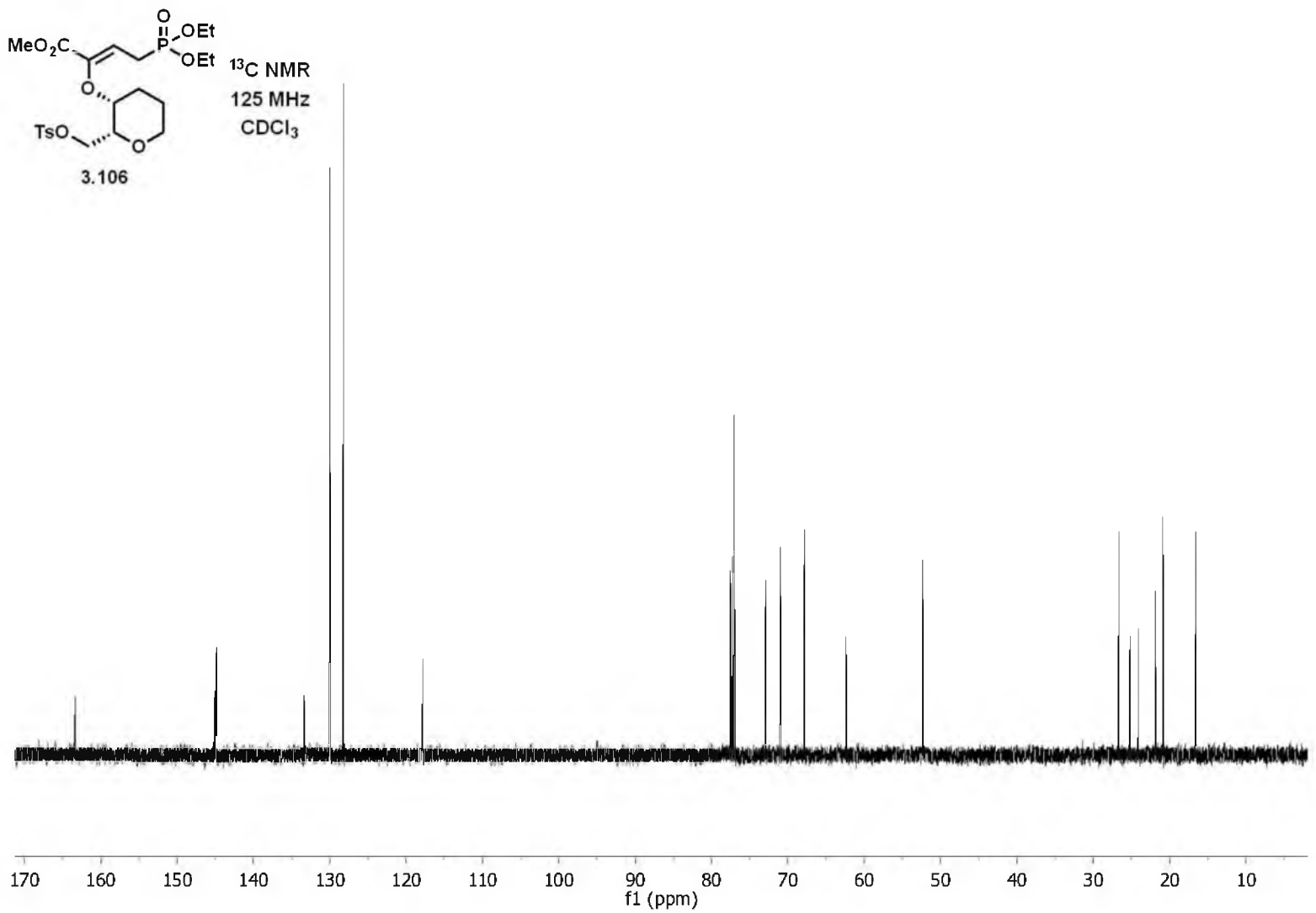


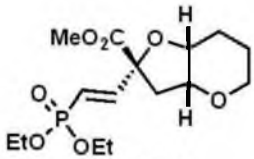
3.106

^{1}H NMR
500 MHz
$CDCl_3$



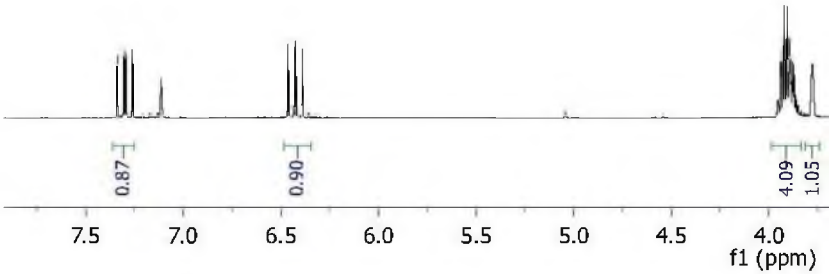

0.93
1.01
1.05
4.19
1.13
3.00
1.08
0.98
2.01
3.12
2.66
0.96
1.09
6.42
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

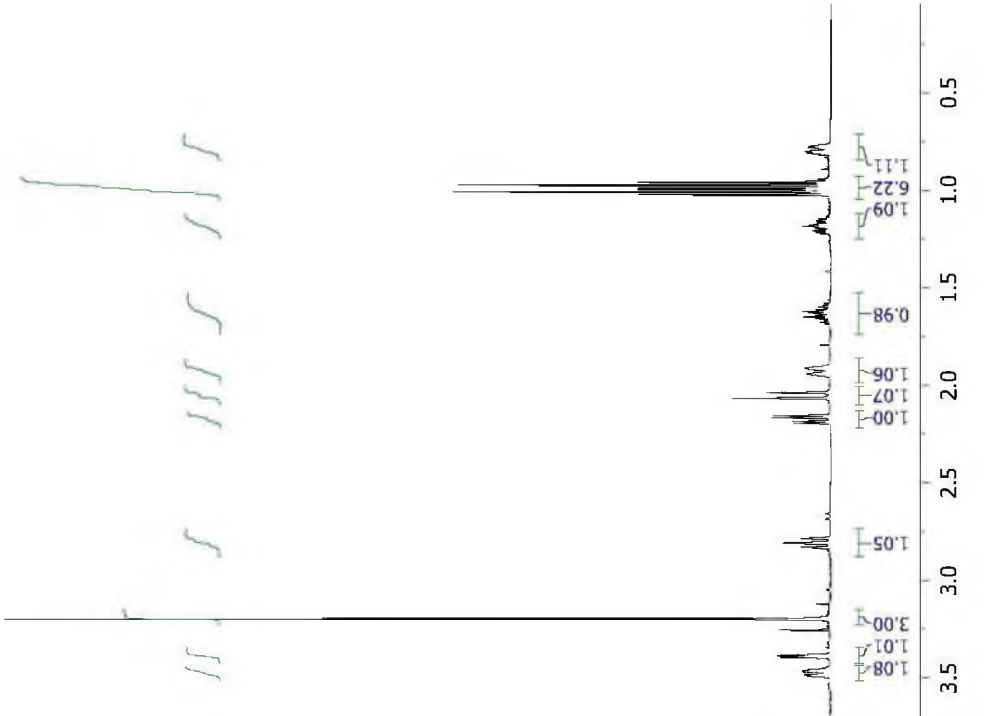

MeO2C
O
P
OEt
OEt
TsO
O
O
3.106
13C NMR
125 MHz
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

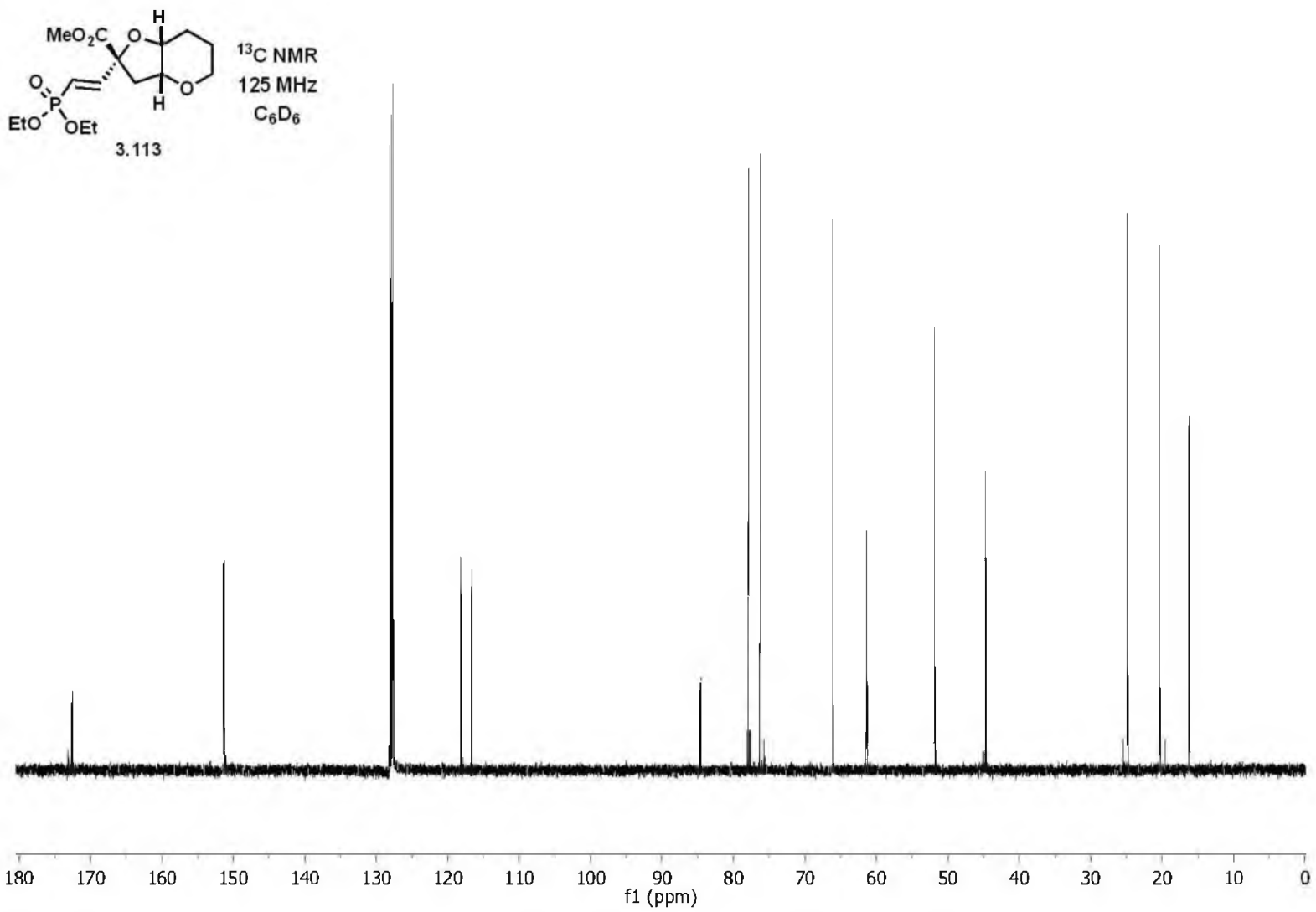


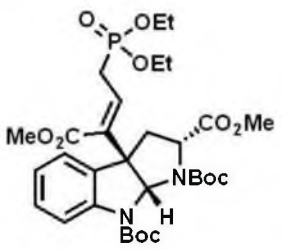
3.113

^{1}H NMR
500 MHz
C_6D_6



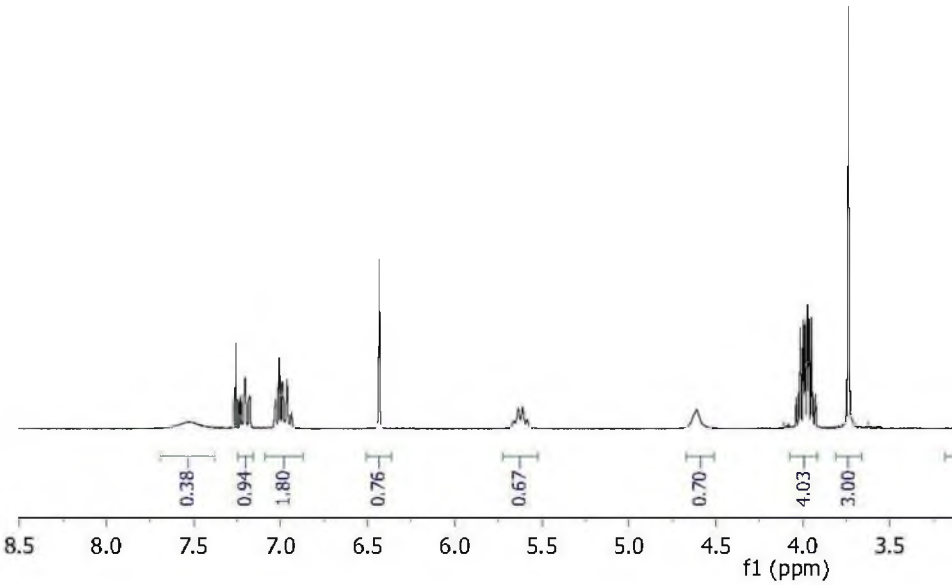

3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.08
1.01
3.00
1.05
1.00
1.07
1.06
0.98
1.09
6.22
1.11

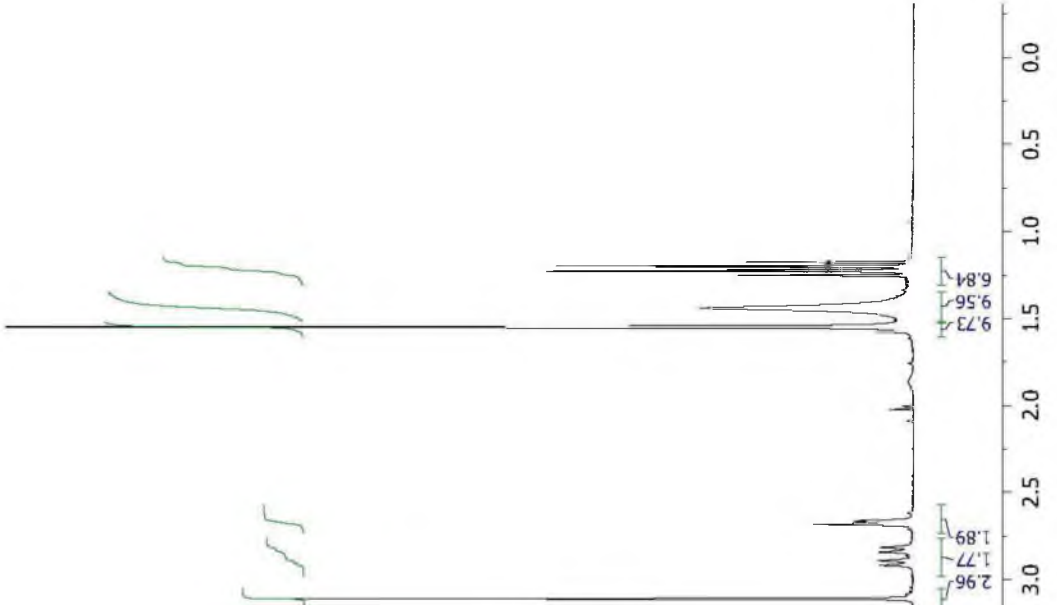

MeO2C
O
H
O
P
EtO
OEt
H
O
3.113
13C NMR
125 MHz
C6D6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

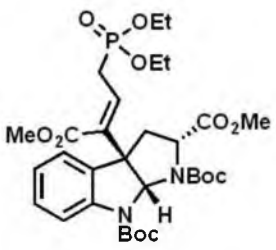


4.10

^{1}H NMR
300 MHz
$CDCl_3$

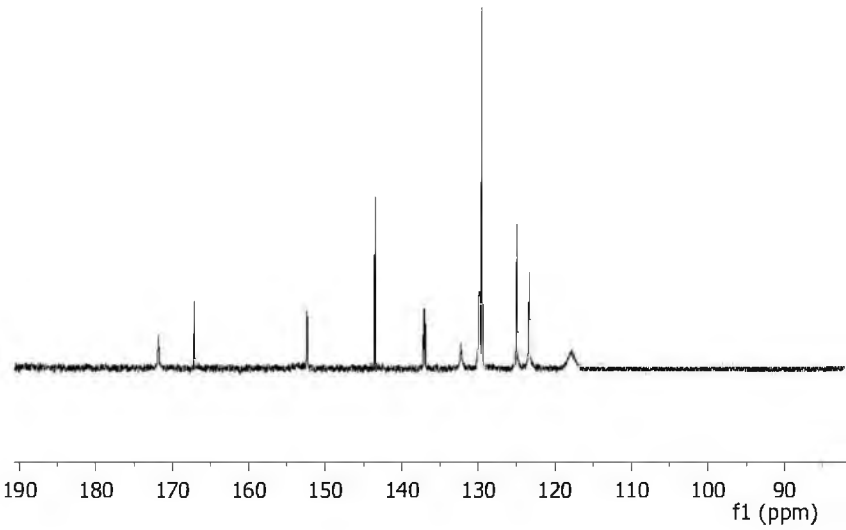


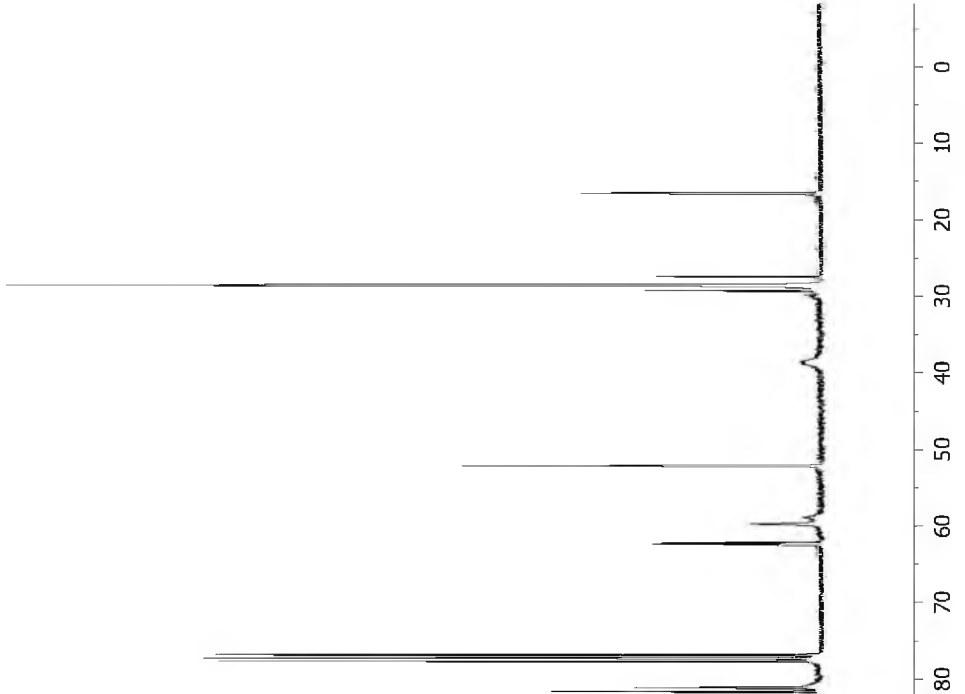

6.84
9.56
9.73
1.89
1.77
2.96
0.0
0.5
1.0
1.5
2.0
2.5
3.0

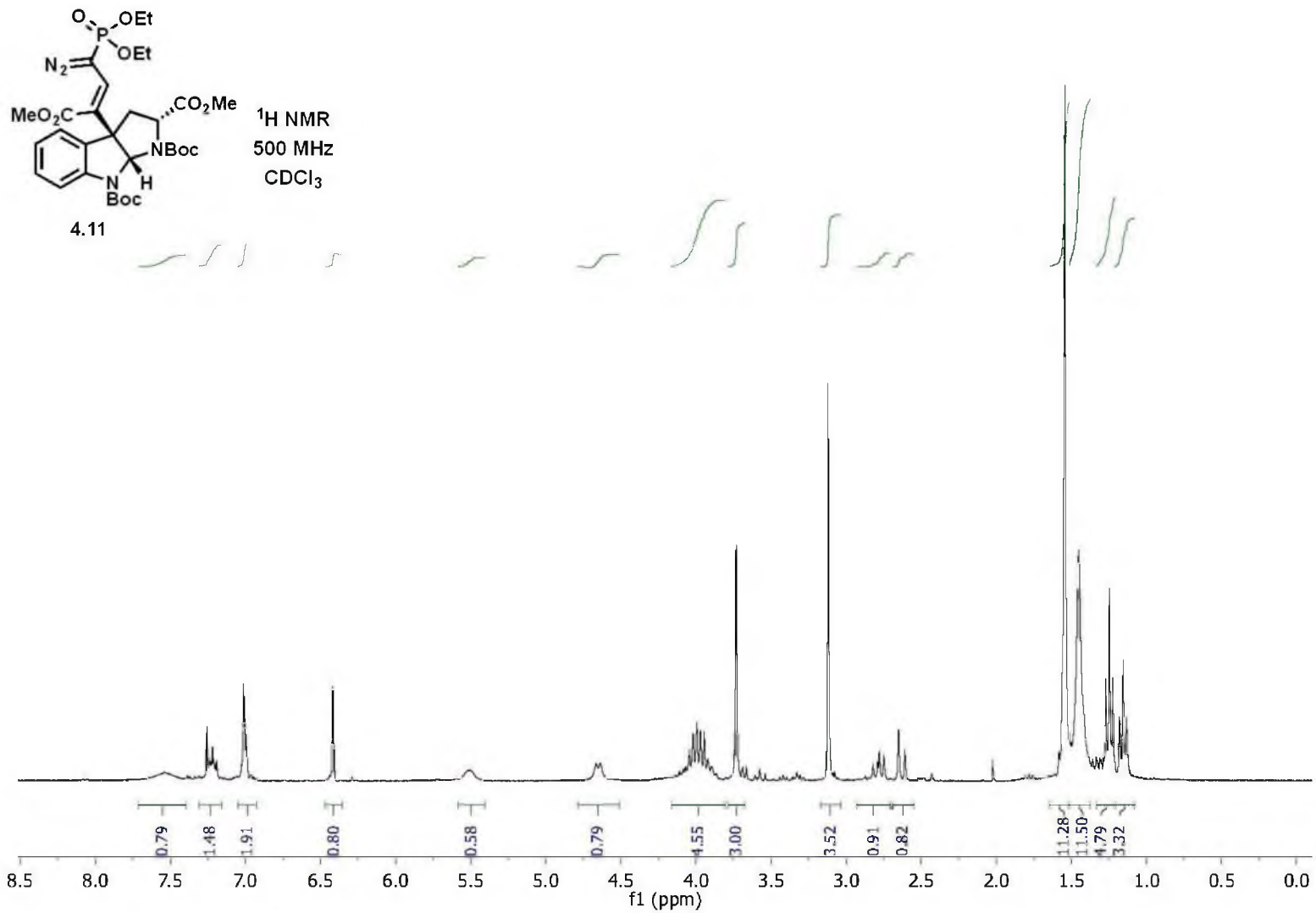


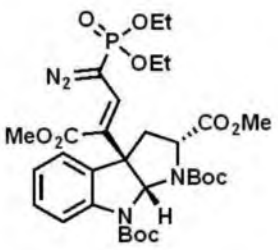
4.10

^{13}C NMR
75 MHz
$CDCl_3$



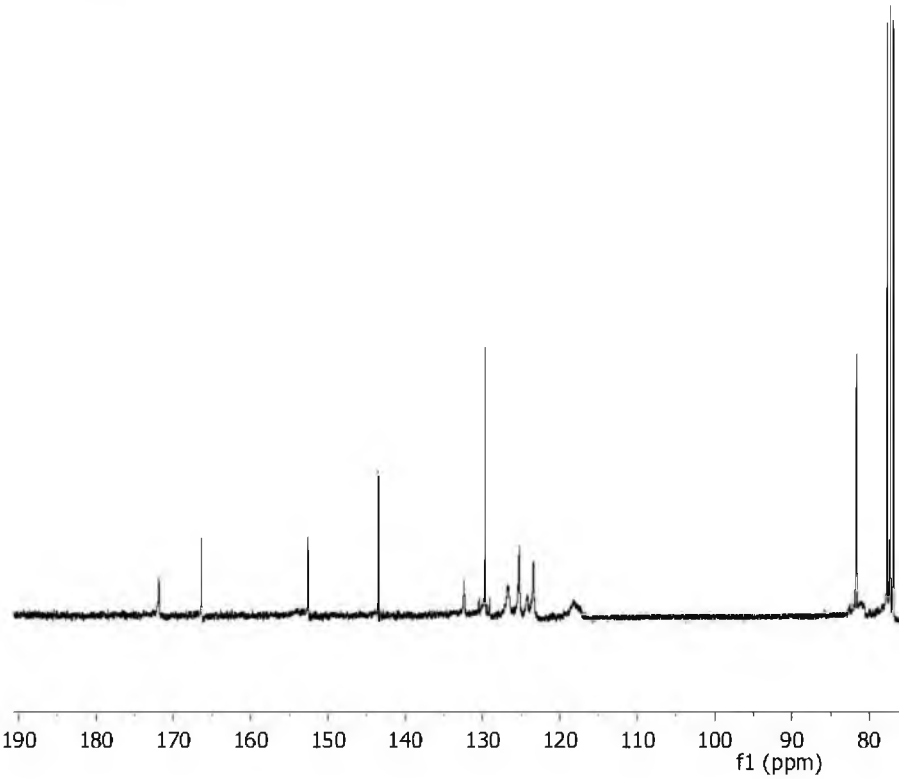

0
10
20
30
40
50
60
70
80


O
OEt
P
OEt
N2
MeO2C
CO2Me
NBoc
N
H
Boc
1H NMR
500 MHz
CDCl3
4.11
0.79
1.48
1.91
0.80
0.58
0.79
4.55
3.00
3.52
0.91
0.82
11.28
11.50
4.79
3.32
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

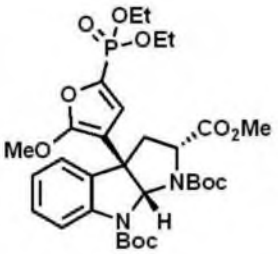


4.11

^{13}C NMR
75 MHz
$CDCl_3$

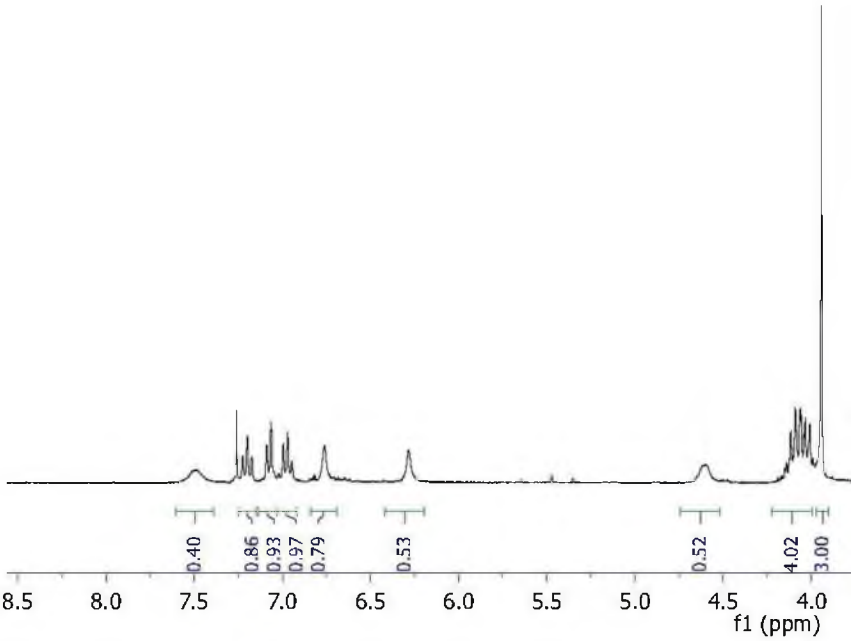


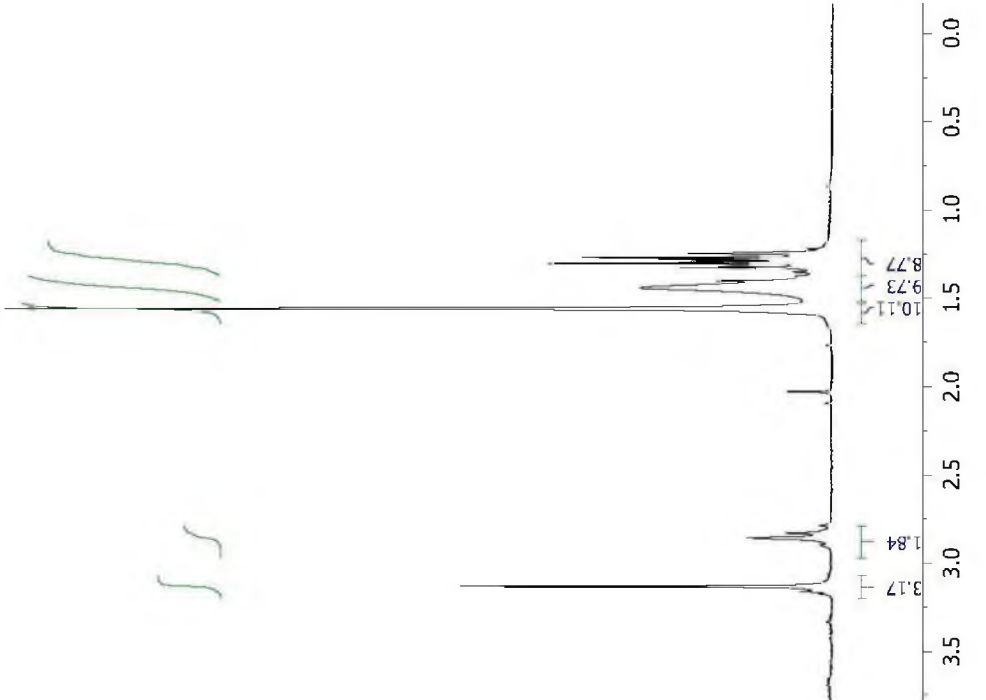

0
10
20
30
40
50
60
70

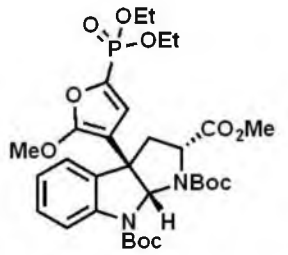


4.12

^{1}H NMR
300 MHz
$CDCl_3$

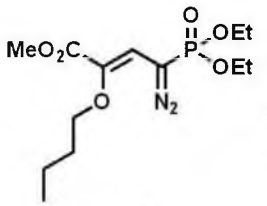



0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
10.11
9.73
8.77
3.17
1.84



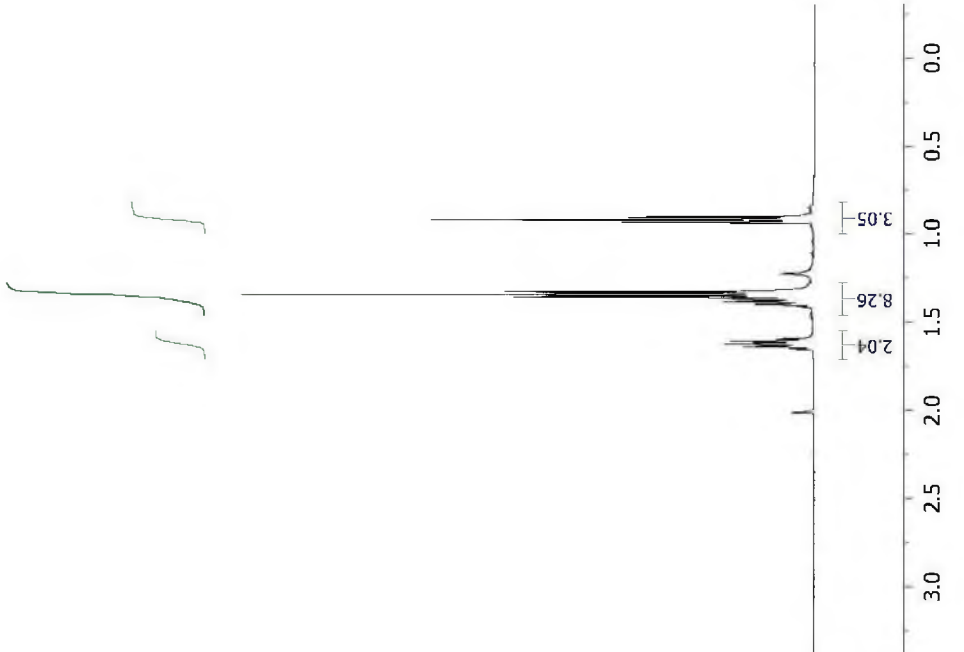
4.12

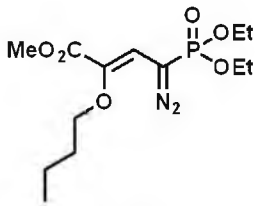
^{13}C NMR
75 MHz
$CDCl_3$



4.15

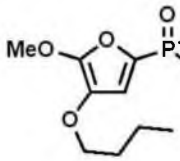
^{1}H NMR
300 MHz
$CDCl_3$


3.05
8.26
2.04
0.0
0.5
1.0
1.5
2.0
2.5
3.0



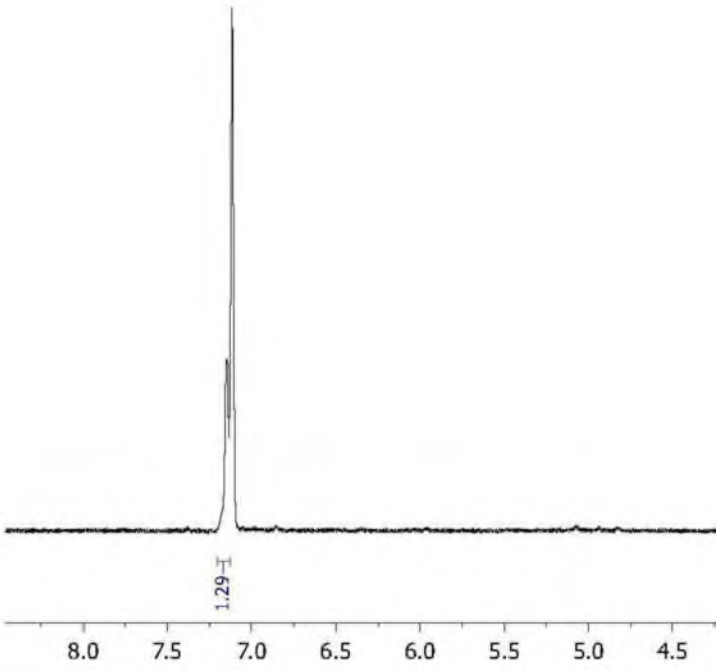
4.15

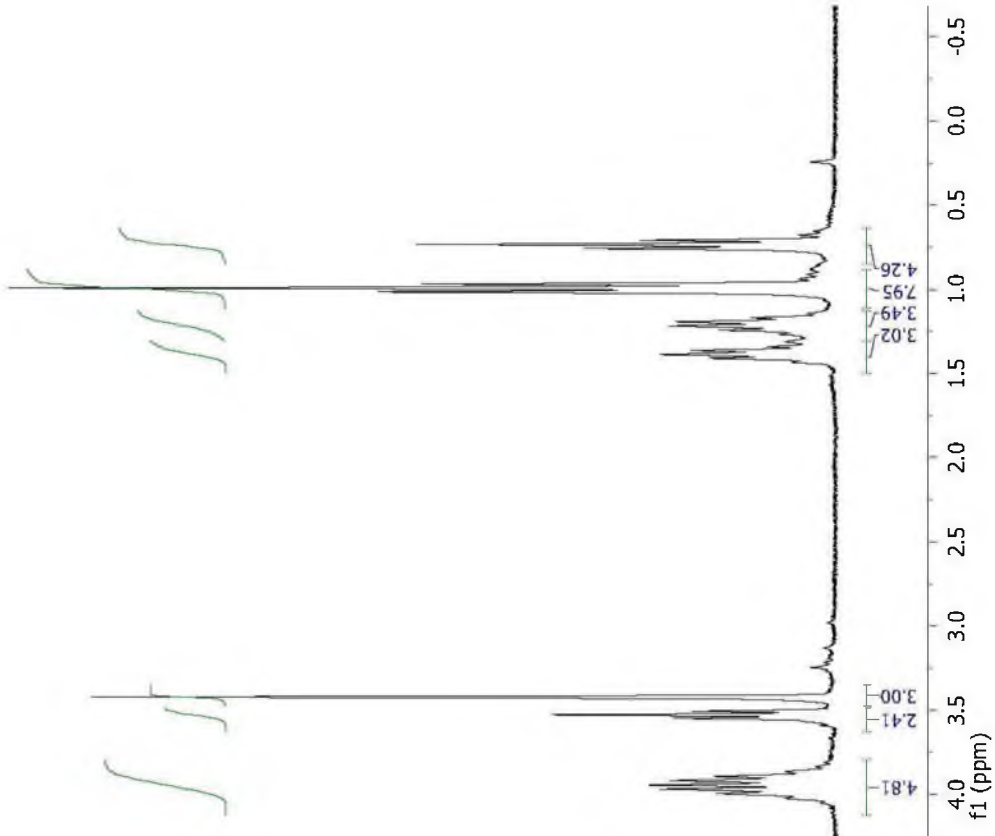
^{13}C NMR
125 MHz
$CDCl_3$

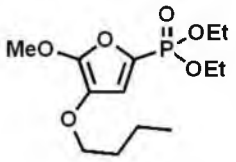


4.16

^{1}H NMR
300 MHz
C_6D_6

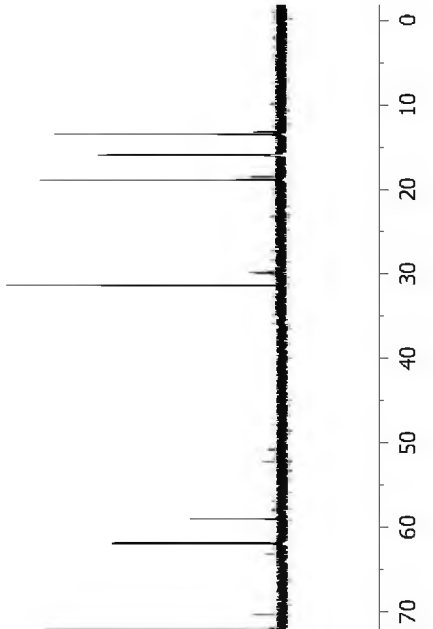



4.81
2.41
3.00
4.26
7.95
3.49
3.02
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



4.16

^{13}C NMR
100 MHz
C_6D_6


0
10
20
30
40
50
60
70